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TRANSACTIONS OF THE AMERICAN ASSOCIATION OF ~~GENITO-URIN~~ARY SURGEONS

VOL. LI 1959

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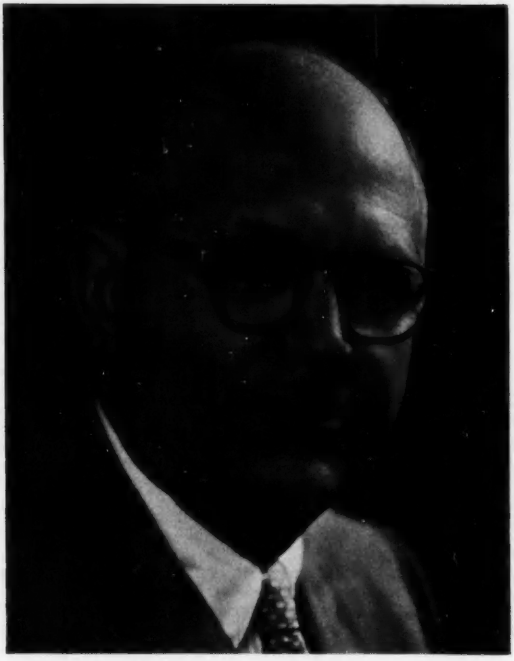


WILLIAM JESSE BAKER
1894–1958

On December 3, 1958, American urology and the urologists of Chicago lost one of their most enthusiastic and active members. Due to a rather sudden cardiac ailment, William J. Baker, commonly known as "Bill," was taken from our midst. He was born in Dallas City, Ill. on May 1, 1894. He obtained the degree of Bachelor of Science from Knox College in Galesburg, Illinois in 1917; the M.D. from Rush Medical College in Chicago in 1923. In the interim, Bill served in the Enlisted Medical Corps of the United States Army, both at home and abroad.

After his graduation from Rush, he served his internship and resident-training at Cook County Hospital from 1924 to 1926. Shortly after this, he became associated with Dr. Harry Culver, which association continued until Dr. Culver's retirement some years ago.

He was appointed clinical assistant in the Department of Urology of Northwestern University Medical School in 1928, and was gradually advanced in rank step-by-step until he was made a full professor in 1954. He was associate urologist at Cook County Hospital from 1932 to 1937,

attending urologist from 1937 to 1952 and chief of the Department of Urology from 1952 until his death. At the same time, he was on the urological staff at St. Luke's Hospital from 1928 and was senior attending urologist since 1946.

Despite the fact that Bill was in his sixty-fifth year, he had every plan for the future to continue his most active and productive life. He had recently rewritten the examination for the County Attending Staff and planned to devote another 7 years of active work in urology at that institution. Due to the affiliation of St. Luke's with Presbyterian Hospital, he was about to sever his connection with Northwestern University Medical School and assume a position as clinical professor of urology at the University of Illinois Medical School.

Bill was a man of many parts. He had great enthusiasm and very decided opinions as to what was right and what was wrong. There was never any question in one's mind as to how he stood on any particular subject. His service record was one of great excellence. He served in the Medical Corps of the U. S. Army as a Sergeant with Base Hospital No. 12 in France from May 1917 to March 1919, following which he returned to Rush Medical College where he graduated in 1923.

In World War II, he entered the Medical Corps very early, and became a lieutenant colonel. He was associated with the 203rd General Hospital, serving 21 months of overseas duty beginning in 1943. He received the Bronze Star on September 22, 1945 as an award for meritorious service in connection with military operation. In June of 1957, Bill received a distinguished service award from his alma mater: Knox College.

He was always actively interested in the organizational side of medicine, and urology in particular. He belonged to the Chicago Urological Society, the North Central Section of the American Urological Association, in both of which he served as secretary and as president. He was president of the American Urological Association at its New Orleans meeting in 1958. He was a member of the American Association of Genito-Urinary Surgeons, the Clinical Society of Genito-Urinary Surgeons, and attended the International Urological Society in Stockholm, Sweden during the summer of 1958 at which time I had the pleasure of visiting with him on several occasions.

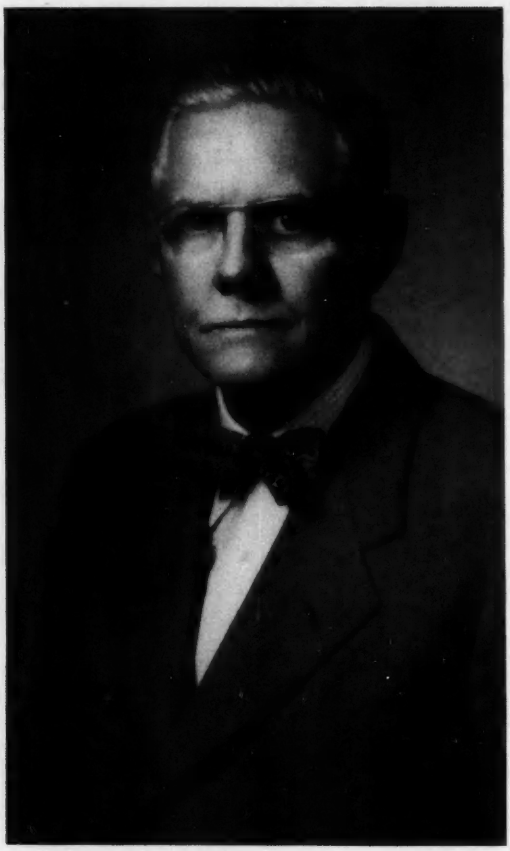
He was a fellow of the American College of Surgeons; also of the International College of Surgeons, and, of course, of the American Medical Association. He was a member of Tau Kappa Epsilon, Delta Sigma Rho, Nu Sigma Nu, Alpha Omega Alpha and Psi Kappa Epsilon. He was a Congregationalist by religion and a member of the Masonic Order. He was a member of the Board of Trustees of the United Church of Hyde Park, Chicago. He belonged to the University Club and the South Shore Country Club, and, I believe, in earlier years, belonged to several other local clubs.

Among Bill Baker's outstanding characteristics were his frankness and his determination to attempt to have everything work out in what he, himself, felt was the proper manner. He had a very excellent manner with medical students, and for many years he and Dr. Culver conducted a urological clinic at the Cook County Hospital for the Northwestern University senior students. He was a great perfectionist and had no particular time for the student who was bluffing or attempting to get by without putting in the required amount of work.

Those of us in the older age group who have seen the development of American urology as a specialty will especially miss Bill because of his valiant efforts always to elevate the urological specialty to a high plane.

His wife, Eloise, herself a distinguished surgeon, and his two sons remain to mourn his loss with us.

VINCENT J. O'CONOR, SR.



AUSTIN I. DODSON
1891–1959

Austin I. Dodson was born on April 16, 1891, in Sutherlin, Pittsylvania County, Va. His tragic death occurred on February 21, 1959.

Dr. Dodson attended the local grade and high schools in Sutherlin, and in 1912 he was graduated from Fork Union Military Academy. Following this, he entered the Medical College of Virginia, from which he was graduated in 1916. He interned at St. Elizabeth's Hospital in Richmond, Va. until August 1917, when he entered the Navy. Upon his return to civilian life in November 1919, he became surgical assistant to Dr. J. Shelton Horsley at St. Elizabeth's Hospital.

While at St. Elizabeth's he became interested in urology and took postgraduate work at the Postgraduate School of Medicine in Philadelphia. He later confined his work to urology and conducted a very active urological practice in Richmond. In 1931 he became professor of urology at the Medical College of Virginia and served as head of the department until his death

Early in his career, Dr. Dodson won recognition as an outstanding urologist. He served as president of the Richmond Academy of Medicine, and in 1943 he was president of the Mid-Atlantic Section of the American Urological Association. He was an active member of the Clinical Society of Genito-Urinary Surgeons, the Southern Medical Association, and the International Urological Association. He served most efficiently on the American Board of Urology, constantly directing his efforts toward raising the Board's standards. He was the first chairman of a committee on postgraduate training, the forerunner of our Residency Review Committee for Urology, which has meant so much to graduate training in urology. In 1956, in recognition of his activities in the surgical specialty, he was elected to the Board of Governors of the American College of Surgeons. Internationally recognized, he attended meetings of the International Urological Association in Athens, Greece, and more recently in Stockholm, Sweden. Only five months ago he presided over the International Colloquium on Resistant Infections of the World Medical Association in New York.

Dr. Dodson made a number of valuable contributions to the literature of our specialty. He wrote the chapter on urological surgery in Bigger and Horsley's OPERATIVE SURGERY. In 1944 the first edition of his textbook entitled UROLOGICAL SURGERY appeared. This book proved so popular that three editions have now been published. Dr. Dodson was co-author, with J. Edward Hill, of SYNOPSIS OF GENITOURINARY DISEASES, the sixth edition of which was published in 1956. He also wrote many scientific articles, dealing particularly with ureteral calculi, surgical technique for implantation of ureters in the bladder, and refined surgical technique for correction of hypospadias.

In 1954 Dr. Dodson's portrait was presented to the dean of the Medical School of Virginia by former residents on his urological service. The presentation was made at a dinner which the residents gave in Dr. Dodson's honor to indicate their affection and high regard for him as a physician and teacher.

He was a member of the Torch Club and the Commonwealth Club of Richmond. He enjoyed fishing, hunting, and gardening. He was president of the Providence Forge Hunting and Fishing Club and a member of the Custis Fishing Club. He was a true Virginian of a quiet, humble nature with a wonderful and unexpected sense of humor.

Dr. Dodson is survived by his wife, Louise Barham Dodson, and two sons, Austin, Jr., and Barham. Dr. Austin Dodson, Jr. has been associated in his father's office for the last two years, and Barham Dodson is a pharmacist in Richmond.

Colleagues throughout the country have been shocked by the ruthless and outrageous manner in which death came to this fine man who contributed so much to our profession.

"And when the stream
Which overflowed the soul was passed away,
A consciousness remained that it had left
Deposited upon the silent shore
Of memory, images and precious thoughts,
That shall not die and cannot be destroyed."

GRAYSON CARROLL

CLARENCE R. O'CROWLEY
1880–1959

During the year we have lost one of the foremost urologists in the United States—one who for many years guided the destiny of the American Urological Association: Dr. Clarence R. O'Crowley—gentleman, friend, and surgeon—dedicated to the ethical and scientific advancement of our specialty, who died at the age of 79 years.

"Clarence," as his many friends affectionately called him, was born in Newark, N. J. In 1897 he graduated from Newark High School where he played football. His college training was interrupted by his service as an Army enlisted man during the Spanish-American War. In 1904 he received his degree of doctor of medicine from Columbia University's College of Physicians and Surgeons and began his practice. When World War I was declared, his joined the Army Medical Corps as a captain.

For 15 years, from 1905 until 1920, Dr. O'Crowley was instructor of urology at the New York Postgraduate Medical School and Hospital.

He also was assistant professor of urology at the Medical School of the University of Pennsylvania for 22 years.

Dr. O'Crowley served as consultant in urology to Clara Maass, Beth Israel, Eye and Ear Infirmary, St. Michael's Hospital, and the Hospital for Crippled Children, all in Newark; Alexian Brothers Hospital in Elizabeth; Perth Amboy General Hospital; West Hudson Hospital, St. Mary's Hospital in Orange; Irving General Hospital, Dover General Hospital, Newton Memorial Hospital, Essex County Hospital in Belleville; The East Orange and Lyons Veterans Hospitals, and the Miles Memorial Hospital in Damariscotta, Maine.

Some years ago he was awarded the Edward J. Ill Award for Extraordinary Service as a Physician and Citizen by the Academy of Medicine of Northern New Jersey. He was past president of the American Urological Association, the New York Urological Society, The American Association of Genito-Urinary Surgeons, the Essex County Medical Society, the Society of Surgeons of New Jersey, and the Essex County Anatomical Society. He was a member of the national medical organizations of this country, and honorary membership had been conferred upon him by the French, the Italian, and the German urological societies. Doctor O'Crowley was also a charter member of the American College of Surgeons, and a diplomate of the American Board of Urology. He was the author of many articles on urology, in which field he pioneered.

The interest of Dr. O'Crowley in the American Urological Association is familiar to all of the older men of this organization. At an early meeting of the American Urological Association he was elected to the Nominating Committee and for 40 years he remained active directly or indirectly in the service of this committee.

Among the older urologists, such as Dr. Braasch, and the late Drs. Bugbee, Kretschmer, Caulk, and Rathbun, he was considered the so-called steering committee.

Although many times he was offered the presidency of the American Urological Association, as he stated in his article, Reminiscences of the American Urological Association (1949), he would not accept the presidency until 1926, for he believed that "other members were more entitled to and more worthy of that great office." In that article he mentioned that he had belonged to the American Urological Association for 42 years and had missed only one annual meeting.

He also paid tribute to The American Association of Genito-Urinary Surgeons, stating that "this group did great and valiant work in raising Urology from the doldrums, and carrying forward in a dignified and elevating manner our specialty, which in those early days had so many aspersions and low remarks hurled at it, and they really set the high standard and respect that urology enjoys today."

Five years ago, Dr. O'Crowley retired from active teaching and practice and moved to Maine.

He is survived by his wife, Mrs. Violet Park O'Crowley; a son, Clarence R. O'Crowley, Jr.; two sisters, and two grandchildren. To them we extend our deepest sympathy.

Although he is no longer with us, those who were privileged to know him and fortunate enough to have his friendship will always remember him.

In the words of Coleridge:

> How well he fell asleep!
> Like some proud river, widening
> toward the sea; calmly and grandly,
> silently and deep, life joined
> eternity.

CHARLES C. HIGGINS

CARCINOMA IN DIVERTICULUM OF FEMALE URETHRA

WM. NILES WISHARD, JR., MYRON H. NOURSE AND J. H. O. MERTZ

From the Department of Urology, Indiana University School of Medicine, and Indianapolis Methodist Hospital, Indianapolis, Ind.

Our purpose in writing this paper is to show that carcinoma in a female urethral diverticulum is not a freak of anatomical location, as it appeared to be in a former presentation before this association, but is a definite clinical entity. We believe that it is not as rare a disease as the 10 known cases would lead one to suspect, but that if it were observed earlier it could be recognized more often for what it truly is. We believe that some advanced cases of urethral carcinomatosis may have originated in a diverticulum (as is evidenced by one of our cases) only to destroy the normal architecture to such an extent that the true source of origin is missed. We further believe that there must be some examples of this disease which have not seen the light of publication, perhaps because of lack of awareness that it exists or of recognizing it.

According to the literature it required about 140 years for urethral diverticulum to become a well recognized, commonly encountered, entity, but we hope that it will not take that long for the subject under discussion. From 1786, when William Hey[1] operated upon Ann Miller in the General Infirmary of Leeds by vaginal incision after which he packed the cavity with lint resulting in a cure, until 1951 the literature on urethral diverticulum became well established, *chiefly* during the second quarter of this century. It was not until 1951,[2] however, that we find any mention of carcinoma in a female urethral diverticulum. Textbooks prior to that year call attention to the possibility of tumor formation but give no authoritative citation in their bibliography. Primary carcinoma of the female urethra, a relatively rare lesion (with 562 examples) was first reported in 1833.[3]

[1] Hey, Wm.: Practical Observations in Surgery. Philadelphia, 1805, p. 305.

[2] Hamilton, J. D. and Leach, W. B.: Adenocarcinoma arising in a diverticulum of the female urethra. Arch. Path., **51:** 90, 1951.

[3] Boivin, M. A. V. G. and Dugés, A.: Traitè Pratique des Maladies de Uterus et de les annexes. Paris, 1833, p. 648.

In May 1951[4] we gave what we thought at the time was the first report of the disease only to find a few weeks later that it had been well described 4 months earlier by Hamilton and Leach.[2] Their report therefore becomes the first, and their patient the first one to undergo operation for this disease (1948). Their patient, aged 53, suffered from stress incontinence and vaginal bleeding. The diverticulum was removed through the vagina and contained soft tumor tissue which proved to be adenocarcinoma. The diverticulum was congenital (smooth muscle walls with cuboidal lining). The tumor, like those in the urethra, may have originated from periurethral glands. Preoperative x-ray therapy was used. Recurrence in the vagina and urethra was treated by curettage and radium. Sixteen months later the patient was free of tumor. A preoperative urethrogram showed the diverticulum.

Our first patient with cancer in a urethral diverticulum was reported 8 years ago.[4] She is alive and free of recurrence although she does have complete loss of her urethra except for a half a centimeter at each extreme end. Her control is good.

Our second patient, not reported in our former paper, was 43. We last saw her in 1958. Several years earlier Dr. Wm. Sigmund had found a urethral diverticulum containing grade 3 epidermoid carcinoma, which was treated by excision. The tumor recurred with ultimate vaginal and pelvic extension. Irradiation did not control the lesion. A urethrovaginal fistula developed. The patient had retention which was relieved by permanent cystostomy. Intractable pain was finally relieved only by cordotomy. The patient has recently died. Her entire urethra was so involved that all normal architecture was lost. We believe that some extensive urethral carcinomas, where normal anatomical landmarks are missing, could have started in a diverticulum which was unrecognized at the time.

[4] Wishard, W. N. Jr. and Nourse, M. H.: Carcinoma in diverticulum of female urethra. J. Urol., **58:** 320, 1952.

Roth's[5] patient was a negress of 40 who had hematuria and urethral bleeding. A soft mass was palpable beneath the anterior vaginal wall. Like the preceding patients, when pressure was applied to the vaginal wall, tumor tissue was extruded through the meatus. It proved to be a transitional cell carcinoma. Endoscopy showed involvement of the anterior two-thirds of the urethra. Urethrectomy, partial vaginectomy and permanent cystostomy were done. The patient was well 20 months later.

Brown[6] reported an adenocarcinoma in a female urethral diverticulum. He observed 23 diverticula over a 6½ year period during which he saw about 6500 new urologic patients. This would place the incidence of diverticulum as 1 in every 282 new patients, and of carcinoma in a diverticulum as 1 in every 23. We have seen over 30 urethral diverticula in 6 years with 2 containing carcinoma; an incidence of 1 in 15. Both of these are undoubtedly too high for an average, but are the only available figures we have found.

Brown's[6] patient, also 40, had a history covering 6 years. Symptoms included frequency, burning, stress incontinence, backache and hematuria. A pulpaceous mass was found beneath the anterior vaginal wall, pressure on which extruded purulent material. A sound could be passed into the diverticulum. Urethroscopy revealed an opening of a diverticulum on the posterolateral wall of the urethra. No reference is made to the presence of tumor. A urethrogram was done but the findings not reported. The diverticulum was removed vaginally. Pathologic report showed a smooth muscle wall with transitional and squamous lining. Adenocarcinoma was found projecting into the lumen of the diverticulum and invading its muscular wall. Postoperative urethroscopy 7 months later showed an opening on the floor of the urethra from which pus could be expressed. Granulation tissue was found in the diverticulectomy scar. The scar was excised down to the urethra and radon seeds implanted. Pathologic report showed no recurrence of tumor. Endoscopy 2½ years after operation showed papillary appearing tissue around the fistula which looked like urethritis cystica. Tissue section showed mucosal edema and a moderate degree of atypicality of some of the glandular epithelial cells. This patient and those of Hamilton and Leach and Hinman are the only three with adenocarcinoma.

The above mentioned 4 references are the only ones we have been able to find in the literature pertaining to the subject. By personal communication,[7-11] however, we have learned of 5 additional cases.

Melnick[7] was kind enough to send us data on a patient he reported to the Obstetrical Society of Philadelphia. A woman aged 50 complained of brownish leukorrhea and bloody urethral spotting for 1 year. Dilatation and curettage and cervical amputation previously showed benign findings. In 1957 Melnick found periurethral induration and a mass beneath the anterior vaginal wall. Tumor tissue was seen extruding from this mass into the urethra when endoscopy was performed. Biopsy revealed transitional cell carcinoma. Treatment was by radium only, 12 1 mg. needles being placed in the tumor and paraurethral tissue from the vaginal side for 24 hours. The total dose was 8000 r. An indwelling catheter was used for 7 days following which the patient voided spontaneously. Followup visits demonstrated disappearance of the periurethral induration. Endoscopy showed no tumor remaining in the diverticulum.

Faulkner[8] of Evanston has also kindly informed me about a patient of his. "She was 51 years of age and the diverticulum was located in the mid portion of the floor of the urethra. Upon viewing this area cystoscopically, papillary tumor tissue was seen within the diverticulum. On vaginal palpation the tumor was firm and about one inch in diameter. The surgical procedure entailed removing the diverticulum as well as a large portion of the floor of the urethra. The pathological report disclosed the tumor to be a transitional cell carcinoma which did not involve the wall of the urethra and seemed to be contained within a fibrous wall. No fistula developed after operation, but a small recurrence appeared two years

[5] Roth, A. A.: Carcinoma of female urethra. Ohio St. Med. J., **51:** 872, 1955.

[6] Brown, E. W.: Diverticulum of female urethra: Report of 23 cases with adenocarcinoma in one. Southern Med. J., **49:** 982, 1956.

[7] Melnick, J. L., Philadelphia, Pa. Personal communication, 1958.

[8] J. W. Faulkner, Evanston, Ill. J. Urol., **82:** 337, 1959.

[9] Frank Hinman, Jr., San Francisco, Cal. Personal communication, 1959. Paper to be published.

[10] J. H. Kiefer, Chicago, Ill. Personal communication, 1959.

[11] G. W. Fish, New York, N. Y. Personal communication, 1959.

TABLE 1. *Synopsis of all known cases of carcinoma in urethral diverticulum*

Author	Date Oper.	Age	Symptoms	Physical Examination	Cystoscopy	Urethrography	Treatment	Pathology	Recurrence	Result
Hamilton and Leach[2]	1948	53	Stress incontinence, irreg. vaginal bleeding 1 yr., regular for 2 wks.	Cystic structure 3 cm. in diam. beaneath ant. vag. wall. "Brain like" tissue on cath. tip	Opening post. ureth. Divert. contained "brain like" material. Cath. would enter soft tumor confined to divertic.	Sac 9 cm. in diam.	Preop. x-ray 1000 r. Surg. removal through vagina. Post op. recurrence treated by radium and excision	3.9 by 3 by 1.9 cm. in size. Fragments of tumor were soft and 4.5 cm. in diameter. Adenoca. Divertic. had cuboidal lining with smooth muscle walls which were invaded	Yes. In vagina and urethra	Cured 16 mos. later. Good functional result
Wishard and Nourse[4]	1949	39	Irritable bladder, hematuria, meatal bleeding, retention, dyspareunia	Cystic mass 3 cm. in diam. beneath ant. vag. wall. Pressure extruded tumor	Opening 0.5 cm. in diam. post. urethra with mucoid tumor tissue protruding; 30 cc expressed, grade 1; transitional cell ca.	Not done	Excision	3.7 by 2.8 by 0.9 cm. in size. Sac had muscular walls and tumor arose from stalk penetrating into walls. Transitional cell ca. Cuboidal lining	None	Cured 7 yrs. Had permanent urethrovaginal fistula. Good functional results
	1958	43	Vaginal bleeding, retention	Vagina full of tumor tissue with loss of normal architecture	Originally had tumor in urethral diverticulum. Later entire urethra (and vagina) involved.	Not done	Excision, irradiation. Cystoscopy. Cordotomy	Epidermoid carcinoma grade 3	Yes	Died 1958
Roth[5]	1954	40	Hematuria and urethral bleeding	Soft mass beneath ant. vag. wall. Pressure extruded tissue	Urethra also involved from point ½ cm. distal to vesical orifice	Not stated	Urethrectomy, partial vaginectomy and cystostomy	Transitional cell ca.	None	No recurrence 20 mos. later. Permanent cystostomy
Brown[6]	1953	40	Incontinence, irritable bladder, hematuria and backache	Tender pulpaceous mass ant. vag. wall. Pressure extruded pus	Opening on posterolat. surface of urethra. Tumor tissue not mentioned	Made but not reported	Vaginal excision	Adenocarcinoma. Wall of divertic. invaded; projected into divertic. in pap. fashion. Smooth muscle lined divertic. Divertic. epithelium squamous and transitional	None. Developed urethrovaginal fist. Subsequently used radon seeds but path. report neg. for tumor	No recurrence 2 yrs. later. Good functional result in spite of urethrovaginal fistula

Melnick[7]	Treated 1957	50	Bloody urethral spotting and brownish leukorrhea 1 hr.	Induration of urethra and mass 3.5 by 2. by 2. cm. beneath ant. vag. wall. Tissue extruded by pressure.	Cysto recovery of tissue	Not reported	24 1 mg. radium needles placed in tumor and paraurethral tissue from vag. approach = 8000 r. No operation.	Transitional cell ca.	No	Diverticulum still present (not removed) but no tumor in it.
Faulkner[8]	1954	51	Retention, urethral bleeding	Vag. mass 2½ cm. in diam., firm	Papillary tissue in diverticulum	Not reported	Vaginal excision	Transitional cell ca.	Yes, cured by x-ray	Cystoscopy shows no tumor November 1958
Hinman[9]	1958	40	Bleeding after manual evacuation for 5 yrs.	Mass in anterior vaginal septum	Diverticular opening in posterior urethra. No tumor observed endoscopically.	Large diverticular shadow to left of urethra with filling defect	Vaginal excision with postoperative irradiation	Adenocarcinoma? wolffian duct origin	None	Cured so far. No fistula
Kiefer[10]	1955	40	Urethral bleeding and hematuria	Fulness in anterior vaginal septum	Diverticular opening with no tumor seen on one occasion and present on another		Vaginal excision	Transitional cell	None for 4 yrs.	Cured
Fish[11]	Treated 1954 no operation	35	Urethral bleeding and hematuria	Mass in anterior vaginal septum	Tumor seen in diverticular opening in mid urethra	Not made	Radium applied to urethra through Foley catheter. No operation	Grade 3, ? type	None for 5 yrs.	Cured but urethral stricture requires continual dilatation

later which was satisfactorily treated by irradiation. The patient's initial symptoms were those of one day duration of inability to void and bleeding from the urethra."

Hinman, Jr.[9] has been good enough to permit us to add one of his patients, a report of which he will publish. This woman aged 40 complained of a mass in the anterior vaginal septum which she had "milked" manually for many years. The discharge from this procedure eventually became bloody. Endoscopy revealed a diverticular opening in the posterior urethra but no tumor was observed. It was presumed that the bleeding was from granulation tissue in the diverticulum. Urethrography showed a large diverticulum with filling defect. The diverticulum was excised in 1958 in the usual manner. Pathologic examination revealed an adenocarcinoma in the diverticulum. The possibility of wolffian duct origin was raised. Postoperative irradiation was used. So far there has been no recurrence (6 months). No urethrovaginal fistula resulted.

Thanks to Kiefer,[10] we have a report of a patient aged 40, operated on in 1955 by vaginal excision. She complained of meatal bleeding and hematuria. Fulness was found in the anterior vaginal septum. Cystoscopy once showed a diverticular orifice with no tumor and at another time a papillary-like tumor protruding. The cell type proved to be transitional. No recurrence has been found for 4 years.

We are indebted to Fish[11] for information of the first use of radium alone (1954) in the treatment of diverticular carcinoma. His patient, aged 35, also complained of urethral bleeding and hematuria. Again, there was a mass in the anterior vaginal septum. It could be "milked" empty. Urethroscopy showed a diverticulum containing tumor in the midurethra. Radium was inserted in the urethra by means of a Foley catheter. The tumor was undifferentiated, grade 3. No recurrence has been observed but a urethral stricture which developed has to be dilated religiously.

SUMMARY

Carcinoma in a diverticulum of the female urethra is a definite disease entity, probably more common than the 10 known cases would indicate. It is found between the ages of 40 and 50. It originates in the diverticulum but may spread to the urethra. Symptoms are spontaneous urethral bleeding or spotting, together with hematuria. Bladder irritability (due to secondary cystitis) and retention have been observed. Physical examination in all cases reveals a soft mass beneath the anterior vaginal septum. Urethral induration has been infrequent. Pressure on the mass frequently extrudes tumor tissue from the meatus. Panendoscopy reveals the lesion. Urethrography probably would too, but has been reported only twice. We should keep in mind the value of panendoscopy, using an F 28 sheath and not merely rely on looking, but should exert pressure on the vaginal wall at the same time to force out the diverticular contents. The tumor is usually transitional cell type, though adenocarcinoma has been reported thrice and epidermoid carcinoma once. In all instances where the report has been complete, muscular fibers have been found in the wall of the diverticulum and have frequently been invaded with tumor tissue. Epithelial lining of the diverticulum is usually transitional or cuboidal cell type. Unlike carcinoma of the female urethra, the prognosis is usually good. Treatment consists of removal of the diverticulum if the urethra is not involved or more radical measures if it is. Adjunct irradiation may be of help. Radium therapy alone has cured 2 patients. Postoperative urethrovaginal fistulas are frequent, but not productive of serious symptoms.

Since this paper was sent to the publisher Seybold[12] has kindly sent me a copy of a paper he has recently read on "Adenocarcinoma Arising from a Diverticulum of the Female Urethra." He also called our attention to another report (which we have missed in our survey of the literature) by Ritter[13] of a squamous cell carcinoma arising from a diverticulum of the female urethra. In addition to this, a paper of ours[14] has very recently been published which, in part, deals with this subject. The total number of instances of urethral diverticular carcinoma now rests at 12.

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[12] Seybold, H. M.: Adenocarcinoma arising from a diverticulum of the female urethra. Case report read at 1959 meeting of South Central Section of American Urological Association, Inc., 1959.

[13] Ritter, Dale: Primary malignancy of the female urethra. West. J. Surg., **61:** 420, 1953.

[14] Wishard, W. N., Jr., Nourse, M. H. and Mertz, J. H. O.: Diverticulum of the female urethra: With special reference to diverticulum carcinoma. South. Med. J., **72:** 890, 1959.

DISCUSSION

Dr. Frank Hinman, Jr. (San Francisco, Cal.): The reason that I want to show this case is not that I happen to have two slides in my pocket or just one more case to report, but, rather, to suggest that there are two possibilities for carcinomas arising in this area.

One is, as Dr. Wishard has suggested, that they arise either as metaplasia of urethral epithelium or as a glandular proliferation from the ducts. The other possibility is that they arise from the epithelium of Gärtner's duct, which lies on either side of the urethra in the anterior vaginal wall.

A case, which seems to illustrate this latter source, is one which fits into Dr. Wishard's age group.

A woman, 40 years old with a 20-year history, was told by her original urologist not to have the diverticulum operated on since it would render her incontinent.

For the past 5 years, she has been expressing this diverticulum, noting increasingly bloody discharge. This slide demonstrates that the diverticulum runs around anteriorly. On microscopic section, there was this picture (slide), which, if one goes back, one finds what R. Meyer described in 1904.

It would be most interesting to review the patients whom Dr. Wishard has reported in the light of this possibility, since this could be a very reasonable source for urethral carcinoma.

Dr. Joseph H. Kiefer (Chicago, Ill.): I can report one more case, if this will help Dr. Wishard. A woman in her forties complained of bleeding. She was the cause of a little controversy among the assistants doing cystoscopy at the clinic, because at one time one of them saw a diverticulum opening; someone else at another time, a papillary tumor. It was proven that from time to time this tumor would extrude through the diverticular opening. She underwent diverticulectomy without particular difficulty. It was a typical transitional cell tumor in appearance. She had no radiation or other postoperative therapy. She is now 4 years postoperatively without present evidence of any recurrence, apparently well.

Dr. George Fish (New York, N. Y.): I would like to add one more case of carcinoma in a diverticulum in the female urethra to those which Dr. Wishard has so well reported.

A white woman, aged 46, was first seen on May 23, 1952, with a history of slight pain on voiding several months in duration. Examination revealed a growth in a diverticulum of the urethra. A biopsy was reported squamous cell epithelioma. She was treated with 10 mil. radium by means of radium needle and Foley catheter, receiving a total of 720 mil. hours. She was discharged from the hospital on May 31 and seen rarely until 1956 when she had developed a postradiation stricture which required dilatation under anesthesia, and an indwelling catheter. She was again negligent in reporting for treatment and wasn't seen until May 27, 1957, when she again had to be dilated. Again there was a lapse until February 1959 when dilatation under anesthesia, and indwelling catheter were required. Since that time she has been dilated at regular intervals and is doing extremely well with no evidence of recurrence of the tumor. This case, therefore, represents an arrest of the growth for 7 years.

Dr. John L. Emmett (Rochester, Minn.): Dr. Reed Nesbit and I have been talking about discussing a case we have both seen, trying to get a woman to empty her bladder.

In all the experience that I have had with this condition in women, I have never been able to convince myself that it is due to a neurogenic disturbance. It may be, especially postoperatively, but a few years ago, we went over most of the cases we had treated for retention in women. There were somewhat over a hundred, and we couldn't determine any one etiologic factor causing the retention. The one thing we have noticed is that you can't tell by looking in a woman cystoscopically why she should have retention.

This occurs in normal women. The only thing I know is to resect them and hope we get a good result. How many patients can you help? I would say that Dr. John Taylor has been fortunate in getting three good results out of three. I imagine it won't stay quite that high. I would think, looking back over our experience, if we can help about three out of four, that the batting average

is pretty good; and why we can help some and not others, I don't know.

The other point I had in mind was where you are going to resect a vesical neck in a woman. I now tell all women that I am going to resect them in two stages, because I know in 50 per cent of the cases I will have to do that, especially using the cold knife punch. The resection is much easier to do, and you can take out more tissue. You take out 25 pieces, and it looks good, and in four or five days, you can take that much or more and leave a wide vesical neck.

The problem arises as to whether you are going to proceed further distally. One school of thought is that you keep coming out of the urethra. I have had the feeling that, certainly, if there is any rationale to this business, it should be the vesical neck and not the urethra that is causing the obstruction, and I usually widen the vesical neck a great deal and then come out a little more into the urethra.

The next thing is the Irish dividends that can accrue from contractures. Several months or so later, you are surprised that even though you have left a small centimeter of the urethra, you will find that the urethra has grown. You may have taken five or six grams out of that patient, and, yet, the patient is going to void satisfactorily. All we seem to be doing is treating a symptom complex; I don't know the etiology.

DR. RICHARD CHUTE (Brookline, Mass.): Do you do a resection around the bladder?

DR. EMMETT: Oh yes. Most of your obstruction in a woman is above. Somebody is going to ask if you have ever had a vesicovaginal resection. The answer is yes.

DR. DANIEL HIGBEE (Denver, Col.): If you resect the bladder neck completely, in my experience it will be followed by a stricture. This is predominantly true. Therefore, what arrangement do you make to dilate the strictures? Do you find it necessary? How do you handle that situation?

DR. EMMETT: It is wonderful if you can pass sounds. You avoid trouble if you can pass sounds. I hate to get up after Dr. Nesbit. He sent a patient over to us, and we failed miserably. You see those difficult problems, and you don't know why.

DR. REED NESBIT (Ann Arbor, Mich.): In some of these women, who have been unable to urinate satisfactorily or who urinate with great difficulty, I have been unable to determine which are organic and which of them are psychic or psychosomatic problems.

There are two patients I sent to Rochester, Minnesota, and when Dr. Emmett says it is wonderful to have patients in your own locality, I think he is wrong, because I have had several of these women, who keep coming back to Ann Arbor, and I can't get rid of them. I send them to Rochester, Minn. In the two I sent up there I was amazed at the amount of tissue removed there. On one occasion, the report that came back to me said that Dr. Gershom Thompson took out 22 gm. tissue. I can't find that amount in most male patients.

DR. EMMETT: Pieces.

DR. NESBIT: That is a lot of pieces. That woman, and a subsequent woman, who was sent to Rochester, arrived on the day that Dr. Emmet had his gallbladder removed. Neither one of these women urinated satisfactorily. The first had three operations at the Mayo Clinic.

I think some of them have hysterical retention, that you can't cure with a resectoscope.

DR. WISHARD: I just want to thank the 3 men, who have brought up the list to ten, and ask that any of you who know of any more kindly let me know.

TREATMENT OF URINARY DYSFUNCTION FOLLOWING SURGERY

JOHN A. TAYLOR

The treatment of urinary dysfunction following pelvic surgery presents a real problem to the urologist. A great divergence of opinion exists as to etiology and methods of treatment.

One theory suggested by McCrea[1] is that the neurogenic dysfunction is due to either trauma or destruction of the pelvic nerves, and that spontaneous restoration of function, if present, is due to a hereto unknown accessory nerve supply which he describes. Nesbit[2] puts great emphasis on the inherent ability of the smooth muscle of the bladder to develop a state of tonus independently of the nerve supply.

The contrasting theory supported chiefly by Emmett[3] is a non-neurogenic theory, which explains urinary retention as due to a postoperative lack of supporting structures around the urethra and bladder, plus prostatic obstruction. The latter theory does not obtain in the cases presented here, as they are all female patients. They all had had pelvic surgery.

The controversy on treatment centers chiefly around transurethral resection of the vesical neck, with or without tidal drainage. It is surprising to find Comarr,[4] working with Bors where tidal drainage has been used so much, come to the conclusion that he cannot see the necessity for it.

I believe that every means at our disposal should be utilized. In three recent cases presented —all with excellent results—both tidal drainage and transurethral resection of the vesical neck was used. It seems to the writer that the McKenna cylinder offers the simplest solution of tidal drainage and was used in these cases. The vesical neck is resected in its entirety using a Nesbit resectoscope in order to have a finger as a guide.

[1] McCrea, L. E. and Kimmel, D. L.: New concepts of vesical innervation and its clinical application. J. Urol., **71:** 549–553, 1954.

[2] Nesbit, R. M. and Lapides, J.: The physiology of micturition. Eleventh Congress of the International Society of Urologists, vol. 1, pp. 106–116, June 1958.

[3] Emmett, J. L.: Urinary retention from imbalance of detrusor and vesical neck; treatment by transurethral resection. J. Urol., **43:** 692–704, 1940.

[4] Comarr, A. E.: Further observations on tidal drainage. J. Urol., **79:** 1024–1066, 1958.

CASE REPORTS

Case 1. A 50-year old married woman (H. T.) was first seen on July 9, 1958 with a permanent suprapubic cystostomy. She gave a history of having undergone a hysterectomy 11 years earlier. Following hysterectomy, she had immediate trouble with urination, and the end result was a residual up to 150 cc. Because of this persistent residual, she submitted to cystoscopy and the urologist reported a "tenting of the bladder," which he thought was due to adhesions. Consequently on February 17, 1958, the patient was operated upon by her gynecologist, with an attempt being made to free the bladder of adhesions down to the trigone. Following this operation she was unable to void and Foley catheter drainage was instituted for 5 days, when she was put on catheterization twice a day. She was discharged from the hospital on intermittent catheterization, which she did herself. After 2 months, during which time her residual varied between 300 and 360 cc, she was again admitted to the hospital around the first of May, and a suprapubic cystostomy was performed. She was wearing a suprapubic tube when first seen by the writer.

Her general physical examination was essentially negative, and all her reflexes were normal, except for exaggerated knee jerks. An excretory pyelogram showed a normal upper urinary tract. She was admitted to St. Luke's Hospital on July 11, 1958, and put on tidal drainage, which was continued until her discharge on August 3. On July 15, transurethral resection of the vesical neck was performed. At the time of her discharge from the hospital, the residual urine had decreased to 6 ounces. She still was wearing a suprapubic tube.

Because further tidal drainage was thought necessary, she chose to go home with the tidal drainage equipment which she could use herself. Her residual gradually decreased until on September 2, 1958, she was re-admitted to the hospital. There was no residual urine. The tube was removed and the suprapubic sinus resected. She was discharged, healed, on September 16, and has had normal urinary function and no residual urine.

Case 2. A 44-year old married woman, first seen in June 1956, gave a history of having had a radical removal of her cervix because of malignancy 3 years previously. Immediately after that operation urinary retention developed and the patient required catheter drainage for one month. The catheter was then removed and since then she had been able to void only when squatting and exerting great pressure on her lower abdomen. She also had catheterized herself daily.

General physical examination was essentially negative, except for sluggish ankle jerks. On cystoscopic examination 900 cc residual urine was obtained. She was advised then to go to the hospital for treatment but deferred it until November 17, 1958. At that time she had 12 ounces residual urine and could only void by applying external pressure. She was put on tidal drainage and two days later her vesical neck was resected. Tidal drainage was continued until her discharge on November 29, 1958. She has been emptying her bladder since without effort, and was last seen on March 5, 1959.

Case 3. A single woman of 68 years was admitted to the hospital on January 30, 1959, because of thrombophlebitis in her leg. She had had a hysterectomy many years earlier for vaginal bleeding, and since then had had difficulty in voiding. Following treatment of the phlebitis, which included bed rest, she experienced increasing difficulty with voiding until, on February 5, she was in complete retention. She was placed on indwelling catheter drainage and after she became ambulatory, the catheter was removed. She still had to strain excessively to void and voided only a few cubic centimeters at a time. Excretory urography showed a normal upper urinary tract. Observation cystoscopy revealed an atonic bladder with trabeculations of the bladder wall. A cystometrogram showed a typical case of sensory paralytic bladder. She was placed on tidal drainage and after one week underwent resection of the vesical neck. The tidal drainage was continued for another week, after which the catheter was removed. She was able to void without difficulty and had no residual urine. She was tested in the office on March 16, and was emptying her bladder. Comment: It is fair to assume that this patient had had some residual urine since her pelvic operation and that the phlebitis, with resulting lack of ambulation, caused her to go into complete retention.

SUMMARY

Three cases of postoperative urinary dysfunction in women following pelvic surgery have been presented, one having had complete retention, which necessitated suprapubic cystostomy. All 3 patients had restoration of normal function following tidal drainage and transurethral resection of the vesical neck.

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STUDIES ON ETIOLOGY OF CARCINOMA OF URINARY BLADDER

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In 1895 Rehn[1] suggested that there was an association between the occurrence of bladder cancer and exposure to chemicals in the dye industry. Since that time evidence has been accumulating that certain aromatic amines may be carcinogenic for the human bladder. One of the most thorough investigations concerning the causal factors of industrial bladder cancer was that published by Case, Hosker, McDonald and Pearson[2] which indicated that 2-naphthylamine, benzidine and possibly other aromatic amines are responsible for a significant incidence of bladder cancer in man after prolonged exposure. More recent evidence has been obtained by Melick, Escue, Naryka, Mezera and Wheeler[3] that 4-aminobiphenyl may cause bladder cancer in chemical workers. Walpole, Williams and Roberts[4] found that 4-aminobiphenyl would also produce bladder tumors in dogs. The evidence that certain chemicals may cause bladder cancer in man has been summarized by Hueper.[5]

Animal experiments have indicated that it is likely that the bladder carcinogens are o-aminophenol metabolites of aromatic amines.[6, 7] The studies of McDonald and Lund[8] and Scott and Boyd[9] have provided convincing evidence that the carcinogens are carried to the bladder via the urine when 2-naphthylamine is fed to dogs.

The first indication that patients with spontaneous bladder cancer excrete aromatic amines in the urine was published by Ekman and Strömbeck.[10] The possibility that these aromatic amines might arise from tryptophan was suggested by the studies of Dunning, Curtis and Maun[11] and Dunning and Curtis[12] who showed that two strains of rats failed to develop bladder cancer when they were fed acetylaminofluorene, but when the diet was supplemented with DL-tryptophan or indole most of the animals developed bladder tumors. This suggested the possibility that some of the metabolites of tryptophan might be carcinogenic for the bladder of the rat. The chemical similarity between certain urinary

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* American Cancer Society-Charles S. Hayden Foundation Professor of Surgery in Cancer Research.

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[7] Bonser, G. M., Bradshaw, L., Clayson, D. B. and Jull, J. W.: A further study of the carcinogenic properties of ortho hydroxy-amines and related compounds by bladder implantation in the mouse. Brit. J. Cancer, **19:** 539–546, 1956.

[8] McDonald, D. F. and Lund, R. R.: The role of urine in vesical neoplasm. 1. Experimental confirmation of the urogenous theory of pathogenesis. J. Urol., **71:** 560–570, 1954.

[9] Scott, W. W. and Boyd, H. L.: A study of the carcinogenic effect of beta-naphthylamine on the normal and substituted isolated sigmoid loop bladder of dogs. J. Urol., **70:** 914–925, 1953.

[10] Ekman, B. and Strömbeck, J. P.: Demonstration of tumorigenic decomposition products of 2, 3-azotoluene. Acta physiol. Scandinav., **14:** 43–50, 1947.

[11] Dunning, W. F., Curtis, M. R. and Maun, M. E.: The effect of added dietary tryptophane on the occurrence of 2-acetylaminofluorene-induced liver and bladder cancer in rats. Cancer Research, **10:** 454–459, 1950.

[12] Dunning, W. F. and Curtis, M. R.: The role of indole in the incidence of 2-acetylaminofluorene induced cancer in rats. Proc. Am. Assoc. Cancer Research, **2:** 197–198, 1957.

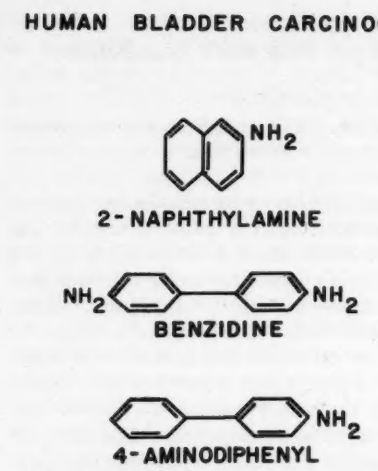

FIG. 1. Chemical structures of aromatic amines which have been reported to cause bladder cancer in man as shown above, resemble several of metabolites of tryptophan (fig. 2).

tryptophan metabolites and the known bladder carcinogens is readily apparent (figs. 1 and 2).

Observations such as these suggested the possibility that patients with spontaneous bladder cancer might excrete abnormally large quantities of one or more of the aromatic amines which are normal metabolites of tryptophan, and that these aromatic amines might be carcinogenic for the human bladder. In other words, patients with bladder cancer might be suffering from a disorder of tryptophan metabolism[13] which might eventually result in the development of bladder cancer. This hypothesis led to the initiation of studies concerning the aromatic amine content of the urine of patients with bladder cancer as compared with normal human subjects.[14, 15] The recent reports from Boyland's laboratories that four tryptophan metabolites produced bladder cancer in mice has strengthened this hypothesis.[16, 17]

[13] Price, J. M.: Disorders of tryptophan metabolism. Univ. Mich. Med. Bull., **24:** 461–485, 1958.

[14] Brown, R. R., Price, J. M. and Wear, J. B.: The metabolism of tryptophan in bladder tumor patients. Proc. Am. Assoc. Cancer Research, **2:** 7, 1955.

[15] Boyland, E. and Williams, D. C.: The estimation of tryptophan metabolites in the urine of patients with cancer of the bladder. Biochem. J., **60:** 5, 1955.

[16] Boyland, E. and Watson, G.: 3-Hydroxyanthranilic acid, a carcinogen produced by endogenous metabolism. Nature, **177:** 837–838, 1956.

Studies in these laboratories were at first concerned with the development of reliable analytical methods which could be used for the quantitative determination of urinary tryptophan metabolites.[18-21] During the development of these analytical methods it became apparent that most of the diazotizable aromatic amines in human urine were tryptophan metabolites.[19] Once these analytical procedures became available, studies were done to determine the quantities of urinary tryptophan metabolites found to be excreted by normal human subjects.[19, 22] It was then found that approximately one-half of the patients with carcinoma of the urinary bladder excreted increased quantities of the aromatic amines and some of the related metabolites derived from tryptophan.[13, 23] In addition to man, it was found that the dog and rat, which also develop bladder tumors, excreted significant quantities of certain of these aromatic amines,[19] while the cat which rarely, if ever, develops bladder cancer[24, 25] excreted very small quantities of chemicals of this type. Similarly, it was found that Turkish cows which develop a high incidence of bladder cancer in certain regions of that

[17] Allen, M. J., Boyland, E., Dukes, C. E., Horning, E. S. and Watson, J. G.: Cancer of the urinary bladder induced in mice with metabolites of aromatic amines and tryptophan. Brit. J. Cancer, **11:** 212–228, 1957.

[18] Price, J. M.: The determination of N-methyl-2-pyridone-5-carboxamide in human urine. J. Biol. Chem., **211:** 117–124, 1954.

[19] Brown, R. R. and Price, J. M.: Quantitative studies on metabolites of tryptophan in the urine of the dog, cat, rat and man. J. Biol. Chem., **219:** 985–997, 1956.

[20] Brown, R. R.: The isolation and determination of urinary hydroxykynurenine. J. Biol. Chem., **227:** 649–652, 1957.

[21] Satoh, K. and Price, J. M.: Flourometric determination of kynurenic acid and xanthurenic acid in human urine. J. Biol. Chem., **230:** 781–789, 1958.

[22] Price, J. M., Brown, R. R. and Ellis, M. E.: Quantitative studies on the urinary excretion of tryptophan metabolites by humans ingesting a constant diet. J. Nutrition, **60:** 323–333, 1956.

[23] Brown, R. R., Price, J. M., Satter, E. J. and Wear, J. B.: The metabolism of tryptophan in patients with bladder cancer. Acta Unio Internat. contra cancrum, in press.

[24] Bloom, F.: Pathology of the Dog and Cat. Evanston: Am. Vet. Publ., Inc., 1954.

[25] Cotchin, E.: Neoplasms of the Domesticated Mammals. Review Series No. 4, Commonwealth Bureau of Animal Health, England, Lamport Gilbert and Co., Ltd., 1956.

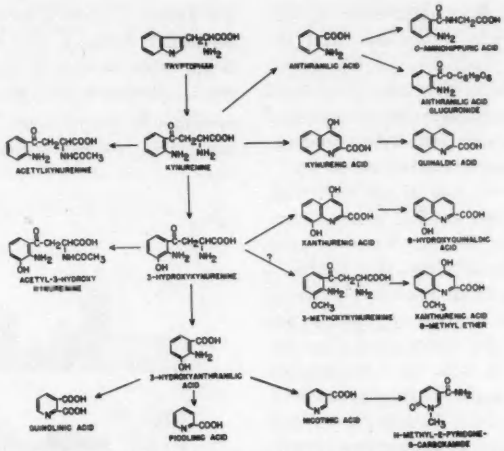

FIG. 2. Interrelationships of metabolites produced in conversion of tryptophan to niacin has been shown in this diagram. It has been reported that 3-hydroxykynurenine, 3-hydroxyanthranilic acid, xanthurenic acid 8-methyl ether and 2-amino-3-hydroxyacetophenone (not included above) produced bladder tumors in mice.[17]

country[26, 27] excreted significantly more acetylkynurenine and less o-aminohippuric acid when tumors were present in the urinary bladder. More recently, evidence has been obtained to indicate that there may be a virus or a similar factor of causal significance in bladder cancer in cattle.[28]

At the present time, therefore, it would appear that the aromatic amines formed from tryptophan and a virus-like agent ought to be considered as two of the possible factors in the etiology of bladder cancer. Some of the details of the studies alluded to above will be presented.

STUDIES ON PATIENTS WITH CARCINOMA OF THE BLADDER

The patients studied were admitted to the urology service of the University Hospitals and many of the urine collections were done in a special metabolic research ward under the supervision of the investigators. The patients were rejected for study for any one of the following reasons: 1) gross hematuria or pyuria; 2) elevation of body temperature above 99.6F; 3) administration of antibiotics, sulfa drugs, or any drugs containing aromatic amines; 4) administration of supplements of vitamin; 5) current or recent x-ray therapy; 6) if the patient was not able to eat an adequate diet; 7) if there was any likelihood of urine loss as a result of nephrostomies or other similar previous surgery; 8) if a histological diagnosis of bladder cancer had not been made at the University Hospitals. The criteria for selection of the patients were so limiting that most of the patients were studied after surgical excision of their tumors.

The metabolic studies were conducted according to the procedure outlined previously.[13] Briefly, at least one 24 hour urine specimen was collected following which 2 gm. L-tryptophan was administered as a single supplement. Following the administration test dose of the amino acid the urine was collected for at least one additional 24 hour period. The control subjects consisted of healthy laboratory personnel and patients admitted to the University Hospitals for relatively minor conditions which would appear unlikely to have any metabolic implications. Since there was no difference in the metabolism of tryptophan by the laboratory personnel as compared with the hospital patients the control subjects were combined into a single group.

[26] Pamukcu, A. M.: Investigations on the pathology of enzootic bovine haematuria in Turkey. Zentr. Veterinarmed., **2**: 409–429, 1955.

[27] Pamukcu, A. M.: Tumors of the urinary bladder in cattle and water buffalo affected with enzootic bovine hematuria. Zentr. Veterinarmed., **4**: 185–197, 1957.

[28] Olson, C., Pamukcu, A. M., Brobst, D. F., Kowalczyk, T., Satter, E. J. and Price, J. M.: A urinary bladder tumor induced by a bovine cutaneous papilloma agent. Cancer Research, **19**: 779–782, 1959.

The excretion of tryptophan metabolites by this group of control subjects before and after the administration of the test dose of the amino acid has provided a range of values which have been regarded as normal. The results obtained with the patients were compared with this range of values obtained from the control subjects.

Thirty control subjects and 41 patients with bladder cancer have been studied in this manner. Of the 41 patients, 20 were found to have abnormal tryptophan metabolism. The patient's metabolism was considered abnormal if there was an excretion value for one or more of the urinary metabolites of the amino acid after the administration of a test dose of L-tryptophan which was outside the upper limits of normal for that particular metabolite. Usually there was an increase in the excretion of kynurenine, acetylkynurenine, kynurenic acid and 3-hydroxykynurenine rather than an increase in only one of this group of metabolites. The excretion of the other urinary metabolites of tryptophan was almost invariably in the normal range for all of the patients. Twenty-one of the patients metabolized tryptophan in a manner which was essentially identical with that of the controls. These results have been published in greater detail elsewhere,[13, 23] but a brief summary of the data has been presented here (fig. 3, *A*). The patients with bladder cancer and abnormal tryptophan metabolism excreted about five times as much kynurenine, twice as much kynurenic acid, and three times as much acetylkynurenine and hydroxykynurenine as did the controls. Those patients with normal tryptophan metabolism excreted essentially normal quantities of these metabolites in the urine. The quantities of metabolites excreted following the administration of a dose of 2 gm. of tryptophan was an exaggeration of the difference that existed in the two groups of subjects so far as basal excretion of these metabolites was concerned (fig. 3, *B*). Those patients with abnormal tryptophan metabolism excreted larger basal quantities of many of these metabolites than did the subjects with normal tryptophan metabolism. Thus, it was found that about half of this group of patients with bladder cancer had abnormal tryptophan metabolism characterized by a quantitative and qualitative difference in the response to a loading dose of tryptophan.

Attempts were made to correlate tryptophan metabolism with a number of clinical features of the disease. These observations have been summarized in table 1. The average age of the patients with normal metabolism was about 67 years, whereas those with abnormal metabolism averaged 60 years of age. There seemed to be no correlation between tryptophan metabolism and

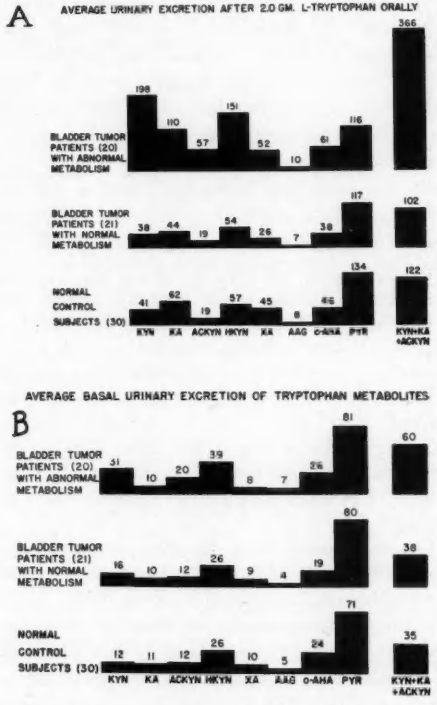
A
AVERAGE URINARY EXCRETION AFTER 2.0 GM. L-TRYPTOPHAN ORALLY
BLADDER TUMOR PATIENTS (20) WITH ABNORMAL METABOLISM
198 110 57 151 52 10 61 116 366
BLADDER TUMOR PATIENTS (21) WITH NORMAL METABOLISM
38 44 19 54 26 7 38 117 102
NORMAL CONTROL SUBJECTS (30)
41 62 19 57 45 8 46 134 122
KYN KA ACKYN HKYN XA AAG o-AHA PYR KYN+KA +ACKYN
B
AVERAGE BASAL URINARY EXCRETION OF TRYPTOPHAN METABOLITES
BLADDER TUMOR PATIENTS (20) WITH ABNORMAL METABOLISM
31 10 20 39 8 7 26 81 60
BLADDER TUMOR PATIENTS (21) WITH NORMAL METABOLISM
16 10 12 26 9 4 19 80 38
NORMAL CONTROL SUBJECTS (30)
12 11 12 26 10 5 24 71 35
KYN KA ACKYN HKYN XA AAG o-AHA PYR KYN+KA +ACKYN

FIG. 3. *A*, comparison of urinary excretion of several tryptophan metabolites by group of 30 control subjects and 41 patients with bladder cancer. Patients with tumors were classified in one of two groups according to their response to loading dose of 2.0 gm. L-tryptophan. Average level of excretion of each metabolite has been given for each group of subjects as number of micromoles (number above bars) excreted in 24 hour period following ingestion of tryptophan. KYN, kynurenine; KA, kynurenic acid; ACKYN, acetylkynurenine; HKYN, hydroxykynurenine; XA, xanthurenic acid; AAG, anthranilic acid glucuronide; o-AHA, o-aminohippuric acid; PYR, pyridone. KYN + KA + ACKYN beneath bar on right indicates sum of urinary excretion of these metabolites. This figure has been published previously.[13]

B, average basal (before tryptophan loading) excretion of tryptophan metabolites by same groups of subjects as shown in *A*. Significance of numbers above bars and key to abbreviations have been given in *A*. This figure has been published previously.[13]

TABLE 1. *A comparison of certain clinical features observed in the patients with normal or abnormal tryptophan metabolism*

	Tryptophan Metabolism	
	Normal	Abnormal
Number of patients	21	20
Average age	67	60
Number of males	15	12
Number of females	6	8
Grade 1–2 tumors	13	14
Grade 3–4 tumors	8	6
Primary in bladder	19	15
Primary in ureter or pelvis	2	5
Transitional cell tumor	21	19
Squamous cell tumor	0	1
Multiplicity of sites	4	6
Number with diabetes	0	4

the sex of the patient, the grade of the tumors, whether or not the tumor was primary in the bladder, ureter or the pelvis, the histologic type of the tumor, or multiplicity of sites. It was of some interest, but probably was not of significance, that four of the patients with abnormal tryptophan metabolism also had diabetes as a secondary diagnosis, whereas none of those with normal metabolism were afflicted with this metabolic disease.

At the present time it is not possible to explain these biochemical observations. However, it may be stated that if urinary tryptophan metabolites are involved in the etiology of carcinoma of the urinary bladder in man, they probably are not concerned in more than half of the patients studied in this series. It should also be pointed out that it has recently been emphasized that there are disorders of tryptophan metabolism in patients with certain clinical conditions other than bladder cancer.[13]

STUDIES ON THE EXCRETION OF TRYPTOPHAN METABOLITES BY VARIOUS SPECIES OF ANIMALS

When the urine of dogs, cats, rats and humans was analyzed for the various metabolites of tryptophan it was found that the cat excreted almost none of the aromatic amines formed from tryptophan (table 2). On the basis of these studies it was concluded that the apparent rarity of bladder cancer in the cat[24, 25] might be related to the fact that this species excretes very minute

TABLE 2. *A comparison of the urinary excretion of tryptophan metabolites by humans, dogs, cats, and rats. The values have been given as micromoles increase in the excretion of the metabolites per kg. of body weight following ingestion of 0.5 millimoles of tryptophan per kg. of body weight. These results were calculated from data which have been published previously*[19]

Metabolite	Man	Dog	Cat	Rat*
Pyridone	9	0	0	—
Kynurenic acid	7	99	0	174
Kynurenine	17	51	0	72
o-Aminohippuric acid	1	5	1	10
Acetylkynurenine	2	14	0.2	10
Xanthurenic acid	4	1	0	25
Anthranilic glucuronide	0.2	19	0	37
Anthranilic acid	0	1	0	30
% of dose of tryptophan accounted for in the urine	7	44	0.1	29

* The rats were given 5.0 millimoles of tryptophan per kg. body weight.

quantities of the aromatic amines formed from tryptophan. The observations on these species of animals are in agreement with the hypothesis that some of the metabolites of tryptophan may well be carcinogenic for the bladder epithelium.

It appeared desirable to attempt to extend these correlations of the occurrence of spontaneous bladder cancer and the aromatic amine content of the urine. Consequently, a search was made for a high incidence of spontaneous bladder cancer in another species of animal so animals with and without tumors could be studied with respect to the relative amounts of tryptophan metabolites in the urine.

STUDIES WITH CATTLE

Bladder cancer is very common in cattle and water buffalo in certain areas of Turkey, while it is rarely observed in other regions of that country.[26, 27] In collaboration with Dr. A. M. Pamukcu of the University of Ankara studies were conducted with Turkish cattle with and without bladder tumors in a manner similar to that which was used to study patients with and without bladder cancer. Since it was not possible to collect 24 hour urines under field conditions in Turkey, random specimens were obtained and the concentration of urinary tryptophan metabolites was related to the amount of creatinine present. The animals were selected for this study

TABLE 3. *The urinary excretion of tryptophan metabolites by Turkish cows with and without bladder cancer as compared with similar data for American cows. These results have been summarized from a previous publication*[29]

Metabolite	Turkish Cows		American Cows (5)
	Controls (15)	Tumor (25)	
	Mg./gm. Creatinine		
o-Aminohippuric acid	8.7	5.4	17.2
Anthranilic acid	8.4	8.4	4.6
Acetylkynurenine	3.9	6.5	4.3
Kynurenine	3.2	3.7	11.2
Hydroxykynurenine	7.5	9.7	14.8
Kynurenic acid	3.7	4.7	5.3
Xanthurenic acid	3.8	2.8	17.2

by veterinarians who were very familiar with the clinical condition. After the urine samples were collected, about two-thirds of the control and tumor-bearing animals were slaughtered and the clinical diagnosis was verified as correct in every case by gross and microscopic examination of the bladders. The urine samples were acidified after collection and were stored in the frozen state prior to the time that they were shipped to this country by air express. When the urine samples arrived they were promptly analyzed for the metabolites of tryptophan which had been studied in the patients. A summary of the data obtained has been presented in table 3. These results have been summarized from an article which was published elsewhere.[29] A statistical analysis of the data summarized in table 3 indicated that the Turkish cows with bladder tumors excreted significantly more acetylkynurenine and less o-aminohippuric acid than did the control Turkish cattle. The quantity of acetylkynurenine excreted by the American cows was approximately equal to that excreted by the control Turkish cattle. Many of the other aromatic amines formed from tryptophan, however, were excreted in larger quantities by American cows although American cows apparently rarely, if ever, develop carcinoma of the urinary bladder. Therefore, it would appear that acetylkynurenine was the only aromatic amine studied which remains suspect as a possible etiologic factor in bladder cancer in Turkish cattle.

[29] Pamukcu, A. M., Brown, R. R. and Price, J. M.: Tryptophan metabolites in the urine of Turkish cows with urinary bladder cancer. Cancer Research, **19**: 321–325, 1959.

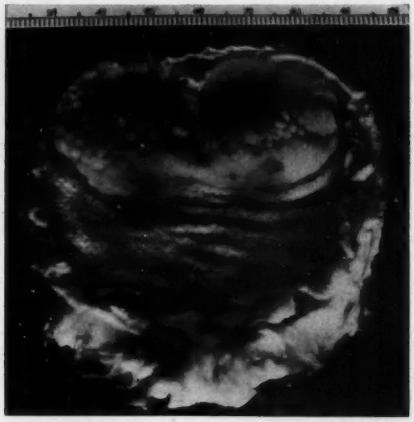

FIG. 4. Typical response to injection of bovine cutaneous papilloma suspensions into bladder wall of calf. Injection was made by suprapubic cystostomy at sites of dark craters 79 days earlier.

The fact that the correlations enumerated above between the occurrence of certain aromatic amine metabolites of tryptophan in the urine and the development of "spontaneous" bladder cancer suggests that these metabolites may play some role in the etiology of carcinoma of the urinary bladder. However, it appears that there must be other factors involved, so studies have been instituted to investigate the possibility that there may be a virus or similar agent concerned with the etiology of bladder cancer.

INDUCTION OF BLADDER TUMORS WITH AN AGENT IN BOVINE CUTANEOUS PAPILLOMAS

So far as the authors are aware no viral agent has ever been implicated in bladder neoplasm. However, in cutaneous bovine papillomas a viral agent has been described.[30] The fact that this agent produced warts of the skin and a fibropapilloma of the genital mucosa of the cow[31] as well as a sarcoma-like lesion of the horse[32] suggested that this agent might also be capable of induction of bladder tumors. Preliminary studies indicate that a suspension of bovine cutaneous

[30] Creech, G. T.: Experimental studies on the etiology of common warts in cattle. J. Ag. Res., **39**: 723–737, 1929.

[31] McEntee, K.: Transmissible fibropapillomas of the external genitalia of cattle. Report of New York State Veterinary College, 1950–51, Cornell University, Ithaca, N. Y., 28, 1952.

[32] Olson, C., Jr. and Cook, R. H.: Cutaneous sarcoma-like lesions of the horse caused by the agent of bovine papilloma. Proc. Soc. Exp. Biol. Med., **77**: 281–284, 1951.

papilloma material was capable of inducing bladder tumors when injected into the wall of the bladder of calves.[28]

The bovine cutaneous papilloma material was preserved at ordinary refrigeration temperatures in 50 per cent glycerol. The papilloma material was then ground to a fine suspension and injected intramurally, in preliminary studies by a suprapubic cystostomy, but subsequently transurethrally using a size 28 Stern-McCarthy working element with an attachable needle. The papilloma suspension was injected either alone or in combination with 3-hydroxyanthranilic acid, 3-hydroxykynurenine or both. These tryptophan metabolites were found to be active bladder carcinogens for the mouse.[16, 17] Carbon particles were suspended in the injection media in order to mark the sites for further study.

At the present time 13 of 15 calves which have received injections of the papilloma agent alone or mixed with the chemicals have developed tumors at the site of injection. The gross appearance of one of these neoplasms may be seen in figure 4. These tumors developed in approximately equal incidence whether the suspension was injected transurethrally or into the bladder under direct visualization and 5 of 6 calves injected with papilloma suspension alone have developed neoplasms. Eight of 9 calves have developed bladder tumors when the papilloma material was mixed with either or both 3-hydroxyanthranilic acid or 3-hydroxykynurenine. The injection of the chemicals alone without the papilloma agent has not been followed by the appearance of neoplasms after observations of up to 170 days.

The reaction to these injections of the papilloma material was followed cystoscopically and some calves were found to have lesions as early as 14 days after exposure. The lesions consisted of a flat type of bullous edema which was limited to the area immediately around the injection site. Later there was a formation of polyps which projected into the lumen of the bladder. In many instances the lesions reached a diameter of 30 to 50 mm. and the tumors from the two injection sites became confluent. In one calf the tumor was estimated at about 40 mm. in diameter at 51 days and has maintained this size for over 300 days. An ulcerated area was usually present in the central portion of the epithelial surface of the tumor (fig. 4) and this region of the tumor was hemorrhagic in appearance. The carbon used to mark the injection site was found in the region of the ulcer-like craters. There was a fibroblastic reaction in the central area of the tumors which was very conspicuous in the older lesions. In these older lesions there was a disturbance of the basement membrane of the epithelium in which there was an intermingling of the epithelial cells with the fibroma-like tissue from the central part of the tumors. These areas resembled early malignant changes, but thus far no gross or microscopic metastases have been found in the regional nodes or elsewhere.

The significance of these lesions is not known at this time. Whether or not an agent of this type might be present in spontaneous bladder tumors in cattle or man has not yet been determined. Further studies will be necessary to determine the fate and significance of the bladder lesions that have been obtained in these calves.

SUMMARY

About half of a group of 41 patients with bladder cancer excreted abnormally large quantities of certain aromatic amines which are urinary tryptophan metabolites. Some of these aromatic amines have been reported to cause bladder cancer in mice.

Humans, cows, rats and dogs, species which develop spontaneous bladder cancer, excreted these aromatic amine metabolites of tryptophan in the urine, while cats, which rarely develop bladder cancer did not excrete detectable quantities of these chemicals.

Turkish cows with bladder cancer excreted significantly higher concentrations of acetylkynurenine, an aromatic amine metabolite of tryptophan, than did Turkish cows without bladder cancer.

These correlations between the levels of urinary aromatic amines and the occurrence of bladder cancer suggest that certain tryptophan metabolites may be naturally occurring endogenous carcinogens analogous to the exogenous human bladder carcinogens of the dye industry.

The recent induction of bladder tumors in calves by the intramural injection of suspensions of glycerol-preserved bovine cutaneous papillomas suggests that there may be a virus or similar factor in the etiology of some bladder neoplasms.

DISCUSSION

DR. FRANK HINMAN, JR. (San Francisco, Cal.): I would like to discuss Dr. Wear's and Dr. Price's paper. This is something that we became interested in 4 years ago in relation to recurrence of bladder tumors after operation. Our experience is entirely different from Dr. Price's, and much of the information which I give you is someone else's rather than our own.

(Slide) I would like to relate Dr. Price's experimental work to our clinical experience since I think the relationship is highly significant. We had found that the incidence of recurrence in areas of the bladder and bladder neck which had previously been resected appeared to be higher than would be expected from chance alone. Howland's figures bear this out: 3.8 per cent primary tumors at the vesical neck, and then 13.3 per cent secondary tumors, indicating that something has changed between the initial observation and resection of the tumor and later observation.

(Slide) There are several possibilities for this recurrence. You are all familiar with missing tumors at the time of resection. Perhaps, there are precancerous changes or infiltration beneath in the submucosa. There could be further carcinogenic action.

We considered the possibility of seeding. A concept occurred to me: The new epithelium that was left behind after the resection or after the injury by the resectoscope could be unusually vulnerable to carcinogens. Here is an interesting area for further research.

(Slide) The new tumor cells *could* settle on the surface. We have studied the viability of these tumor cells after resection, running them through sieves and studying them at varying times. If you use distilled water for the resection, the stain indicates dead cells some 15 minutes after the resection. It wasn't necessary to use phenol or other agents. That leaves us, then, with the concept of facilitated carcinogenesis in the raw areas.

The work I would like to mention is parallel with Dr. Price's. It is that by Bonser, with Boyland and Wallace in London. They have been studying what happens to these carcinogens in the body. It is important to realize that these carcinogens——incidentally, in London, they measure 3-hydroxyanthranilic acid, and this is the principal chemical which they believe to be carcinogenic——are conjugated in the liver to form a glucuronide. They are thus excreted as glucuronides in the urine and are inactive. In the bladder, a glucuronidase releases the active carcinogen. (I understand Dale Scott can't duplicate this.) They have found there is not only an excess of tryptophan, but, also, there is an excess of the enzyme, glucuronidase, which then would be expected to release more carcinogen.

Their line of thinking has a direct therapeutic implication. If one could influence the amount of glucuronidase, the enzyme, one would have less carcinogen. One way this can be done is by giving a lot of fluid. It is interesting that Kennaway, twenty or thirty years ago, found that bar men, who were allowed 2 quarts of free beer a day, had the lowest incidence of bladder carcinoma in the British Isles. The other way to influence the concentration of glucuronidase is to give the patient saccharolactone, a simple compound looking like glucose. The glucuronidase can't distinguish it from the glucuronides. They can reduce the glucuronidase activity by 90 per cent by the administration of saccharolactone.

I just received a letter from Wallace saying they now have 34 patients under treatment with saccharolactone, with what they think are good clinical results, but they are now running a double blind series so they will know in 2 years whether or not this is effective treatment. In the meantime, they are increasing the patient's water intake. Perhaps a trial of this alone would be worth while.

DR. JOHN K. LATTIMER (New York, N. Y.): Does an indwelling catheter produce enough red blood cells to interfere with this determination?

DR. J. M. PRICE (Madison, Wis.): The only reason we are concerned with blood in the urine is because it interferes with the analysis. The use of an indwelling catheter has not produced hematuria or any real difficulties, although most of these patients were studied after their tumors were removed, when there was no reason to use catheters.

We have studied a number of these patients at intervals on subsequent admissions and have

found that those who had abnormal metabolism were abnormal subsequently, whether there was a tumor in the bladder or not. Those who have been normal in this respect have remained normal.

I would like to make one comment on Dr. Boyland's work. In our laboratories we have found that some of these tryptophan metabolites were excreted in the free, unconjugated form. Thus the administration of saccharolactone, a glucuronidase inhibitor, has limited value from a theoretical standpoint, since it cannot inhibit the liberation of already free metabolites.

The other substance that will help reduce the excretion of these metabolites is pyridoxine. We have restudied several of these patients while giving them large doses of pyridoxine, and this vitamin reduced the excretion of tryptophan metabolites in the urine.

Dr. Luis A. Sanjurjo (Santurce, Puerto Rico): I wish to refresh your memories and give a followup on some comments that I made before this society 2 years ago. I refer to a lady who had the left kidney removed in Puerto Rico for a papillary carcinoma of the renal pelvis. She was later on referred to me by the late Dr. Dodson who had removed the ureteral stump and a segment of the bladder for recurrent carcinoma.

During followup cystoscopic studies and until 6 months ago, this patient continued to develop small papillary carcinoma growths in the bladder which were treated endoscopically.

To take care of her urinary infection furadantin was prescribed over a long period of time. It may be coincidental or whatever you wish to call it but since furadantin was prescribed there was no recurrence of tumor.

This happening was brought to the attention of Mr. H. Wahle and Dr. Paul McLeod of Eaton Laboratories and at their suggestions furacin tablets were used instead of furadantin. Forty-five days later the patient had a small recurrence of tumor and the patient was placed back on furadantin.

I do not know the value of these findings, but I pass this information on to you for what it is worth.

Dr. John K. Lattimer (New York, N. Y.): Apropos of the furadantin, the St. Albans Naval Hospital has used this drug, and they have seen no lasting benefit in tumor cases. They tested it with great enthusiasm, but it didn't prove to be of any help.

Dr. Wyland F. Leadbetter (Boston, Mass.): I would like to ask Frank Hinman if he has done any work on destroying cells after transurethral resection to see if there is a reason for using some drug in the bladder.

Dr. Frank Hinman (San Francisco, Cal.): Our trouble is developing experimental methods. In our surgical laboratory we are not equipped for tissue culture, but by using the Schreck technique, we have found that these cells are killed almost immediately by the distilled water, which we old-fashionedly used for transurethral resections of all sorts. Consequently, this doesn't seem to be as great a problem as it would appear. However, what I did when I became concerned about it was use 1:500 phenol solution, which, if there is not too much bleeding, is an effective antiseptic agent. It is in distilled water, and is nonisotonic. This solution, left in the bladder for an hour, would appear to be a practical measure.

Dr. William P. Herbst, Jr. (Washington, D. C.): What dose pyridoxine does Dr. Price suggest?

Dr. Price: From the biochemical standpoint, it reduced the excretion of the amines in the urine.

Dr. Herbst: What dose?

Dr. Price: In an effort to thoroughly overload the patients, we used 100 mg. a day, which is probably more than we needed to use. I would anticipate ten would be adequate, but have no data to support that.

Dr. Joseph H. Kiefer (Chicago, Ill.): At the Atlantic City meetings seven or eight years ago, we reported these recurrences in the urethra, and Dr. Reed Nesbit said maybe it is the difference in the irrigating fluids. We got a young fellow to try the vitol staining technique, which presumably shows living and dead cells. In doing this experiment in urine the cells would survive and would show as being living. They would not absorb the dye. If you used water instead of urine and put it on the microscope, the water always killed the cells. We have just used water as the irrigating fluid when operating on bladder tumors. When we were doing prostatectomies, we used glycine.

CARCINOMA OF THE BLADDER: CHARACTERISTIC MODES OF LOCAL INVASION

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It is now fairly generally agreed that the type of treatment to be chosen for an infiltrating carcinoma of the bladder will depend at least to some extent upon the depth to which this tumor has invaded the wall of the bladder. However, the preoperative estimate of this depth of infiltration cannot be expected to equal in precision the postoperative or postmortem findings based upon the study of the whole thickness of the bladder wall. But any information that might increase the accuracy of one's preoperative estimate should be fully utilized. Preoperative segregation, by biopsy of the bladder wall and bimanual palpation of the bladder, is usually simple in most cases of small superficial tumors and large deep tumors. There are two situations, however, in which misinterpretation of the preliminary findings results in the preoperative classification of the tumor as superficial when in reality it is very deep. These two sources of error are attributable to the manner in which certain tumors invade the wall of the bladder, and the first is illustrated by the following case.

A 56-year-old man (B.U.I. 55800) was referred on December 3, 1956 because of intractable vesical irritability 14 months in duration. In the beginning the urine was sterile and biopsies had shown only chronic inflammation. On admission the only positive findings were pyuria with drug-resistant bacilli, a small bladder capacity, and bullous edema of the trigone and bladder neck. Biopsies again revealed only chronic cystitis. After 7 months of regular treatment with instillations and irrigations scattered areas of splotchy reddening were visible and biopsy of these showed marked epithelial pleomorphism suggestive of noninvasive carcinoma. On October 24, 1957 a number of small papillary tumors were present and these on biopsy were found to consist of poorly differentiated squamous carcinoma invading only the superficial muscle and several nearby lymphatics. The outlook was considered favorable because of only superficial infiltration as disclosed by transurethral biopsies, and on November 11, 1957, the urine was diverted by an ileal loop, and the bladder removed. Retroperitoneal metastases were present. Sections through the bladder wall showed poorly differentiated squamous carcinoma invading as a mass only as far as the superficial portion of the musculature but metastasizing through the lymphatics to the perivesical fat and prostate (figs. 1 and 2). Following discharge from the hospital the patient's course was steadily downhill and he died on January 14, 1958. At postmortem examination widespread metastases were found in nodes, liver, and bone-marrow.

Apart from the apparently unavoidable delay in finding this elusive tumor, the error in judging it to be superficial, and therefore localized to the bladder, lay in the failure to recognize the significance of local lymphatic involvement as shown by biopsy. Whenever such involvement can be demonstrated, the likelihood of intramural metastasis is always considerable.

To see how often tumors metastasized through the bladder wall in this manner, microscopic slides of 303 cases of infiltrating carcinoma of the bladder were critically studied. These sections had been taken from specimens obtained by autopsy, cystectomy, and segmental resection. The cases were separated into the following 4 stages of infiltration: A, submucosa only; B_1, less than halfway through the muscle; B_2, halfway or more through the muscle; C, perivesical fat or prostate. Fifty-one cases had to be eliminated from the 206 in stage C because of insufficient data, leaving 155 in this group. The total series therefore consisted of 252 cases (table 1).

Although the lymphatics were found to be invaded at some level in the bladder wall in 79 cases (31 per cent), they were involved in only seven in which the tumor had failed to extend to the halfway level in the muscle wall. Of these seven, only two, both poorly differentiated squamous cancers, metastasized to a depth greater than that reached by the primary growth. The results of a detailed analysis of the relation-

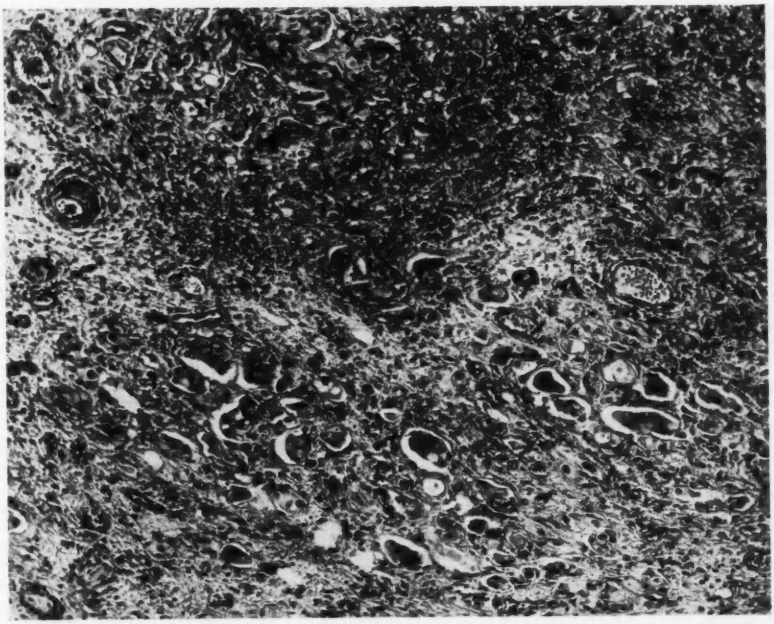


FIG. 1. Poorly differentiated squamous carcinoma on surface with many lymphatics involved in submucosa. S. P. 57-5418. ×100.

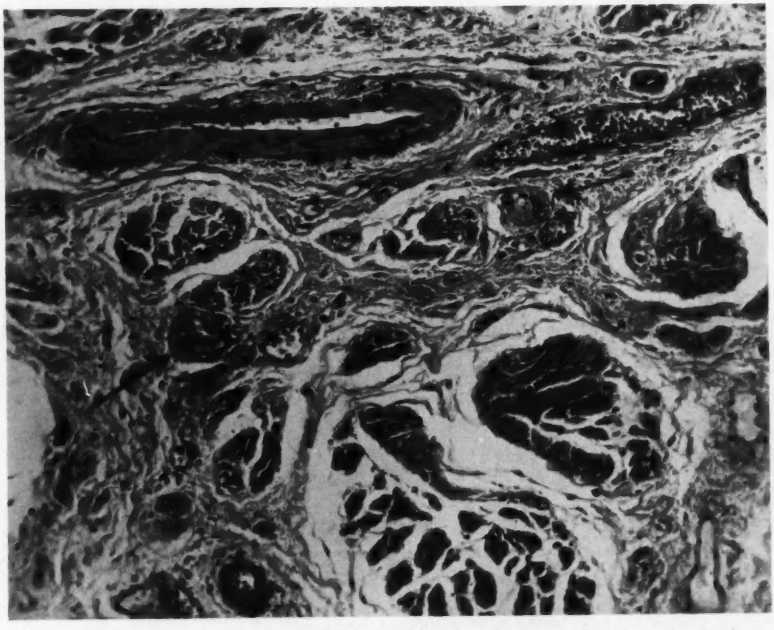


FIG. 2. Same case as figure 1, showing collections of tumor cells within two lymphatics in muscularis. ×150.

ship between the level at which the lymphatics were involved and the depth of extension of the associated mass, together with its cellular characteristics, are shown in figure 3.

Stage C was reached by lymphatic metastasis alone in only eight of the 155 cases comprising that group (5 per cent) (fig. 4), and in only five of its 80 poorly differentiated squamous carcinomas (6 per cent). Furthermore stage C was reached by lymphatic spread in only 3 per cent of all superficially infiltrating tumors (table 2), and in only 8 per cent of those that were highly malignant. But it was reached in two of 12, or 17 per cent, of the poorly differentiated squamous carcinomas confined primarily to stages A and B_1 (table 3). Local lymphatics involved at different levels were as follows: stage A, one in 40 (2.5 per cent); Stage B_1, six in 22 (28 per cent); Stage B_2, 14 in 35 (40 per cent); stage C, 66 in 155 cases (40 per cent) (table 4). These reported levels at which lymphatic involvement was demonstrable included some cases in which the penetration of the primary tumor mass had lagged behind the more rapidly spreading lymphatic metastases. Although the figures show that lymphatics are more frequently involved by tumors that are deep in the bladder wall, it seems likely that intramural lymphatic metastasis would be found more often at all levels if serial sections could be made in each case. Such an undertaking, however, is obviously not practicable. In the biopsy specimens lymphatic involvement always should be searched for, especially when the tumor is believed to be only superficially infiltrating and to consist of poorly differentiated squamous carcinoma.

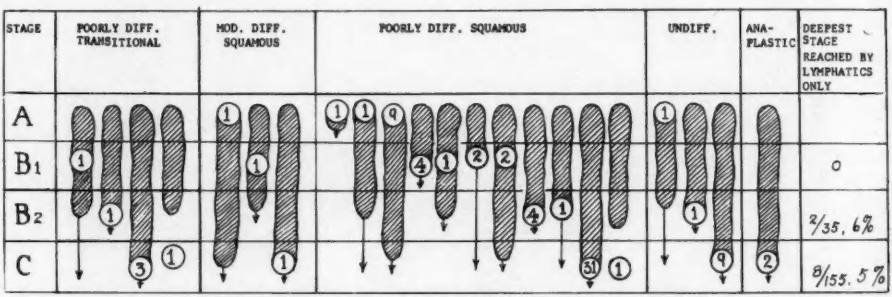
TABLE 1. *Classification of 252 cases of infiltrating carcinoma of the bladder*

Type of Tumor	Stage of Infiltration				
	A	B^1	B_1	C	Total
Well diff. trans.	11	0	0	0	11
Mod. diff. trans.	13	10	4	9	36
Poorly diff. trans.	8	4	6	16	34
Mod. diff squam.	0	3	7	16	26
Poorly diff. squam*.	8	3	14	80	105
Undiff.	0	1	2	24	27
Anaplastic	0		1	7	8
Adeno	0	1	1	3	5
Total	40	22†	35	155	252

* One additional case consisted of a primary mass at stage B_1 but with a cell nest in stage C. This required final classification as stage C.

† One additional case, noted above, classified as stage C, was primary stage B_1.

The second source of error leading to the preoperative miscalculation regarding the true extent of infiltration is also related to the manner in which the tumor invades the bladder wall. Slender finger-like projections of tumor may extend for considerable distances from the primary mass and, when cut at right angles to their axis, appear as isolated masses or nests (fig. 5). If such a strand of tumor takes a tortuous course through the wall, its continuity can be recognized only by serial sections, and a single section might show a solitary clump or nest at some distance from the primary growth.



LYMPHATIC INVOLVEMENT IN 252 CASES OF INFILTRATING CARCINOMA OF THE BLADDER

KEY: - MAXIMUM DEPTH OF INFILTRATION OF PRIMARY TUMOR

(1) - NUMBER OF CASES, AND MOST SUPERFICIAL LEVEL OF LYMPHATIC INVOLVEMENT

↓ - MAXIMUM DEPTH OF LYMPHATIC INVOLVEMENT

FIG. 3

FIG. 4. Deeply infiltrating tumors with lymphatic metastases in stage C. *A*, Path. No. 7742. ×100. *B*, Path. No. 17710. ×150. *C*, Path. No. 12872. ×150. *A*, *B*, *C*, poorly differentiated squamous carcinomas. *D*, Path. No. 25533. ×100. Anaplastic tumor.

TABLE 2. *Lymphatic spread to stage C from tumors in primary stages A and B_1*

Stage	Total Primary Tumors	Stage C	
		No. of cases	Per cent
A	40	0	0
B_1	23	2	9
Total	63	2	3

TABLE 3. *Lymphatic spread to stage C from tumors of high grade in primary stages A and B_1*

Type of Tumor	Total Primary Tumors	Stage C	
		No. of cases	Per cent
High grade	26	2	8
Poorly diff. sq	12	2	17

Our series of 252 cases were therefore studied to see how often such finger-like projections could be demonstrated and what sort of tumors gave rise to them (table 4). In stage A there was none; in stage B_1 there was one. In one other case, in which a primary compact mass was in stage B_1, an isolated nest of tumor cells was found in the perivesical fat, apparently not within a lymphatic. This was one of 12 poorly differentiated squamous carcinomas primarily in stage A or B_1 (8 per cent). In stage B_2 there were six, and in one additional case a moderately differentiated transitional cell carcinoma, which appeared compact, was associated with an isolated tumor nest in the fat.

Table 4 represents a summary of the three characteristic ways in which the tumors were found to penetrate the wall of the bladder. The tendency was for most of them to invade as a more or less compact mass with no significant separation of small clumps or single cells in any direction from the main tumor (70 per cent of 252 cases) (fig. 6). The chief exception was in cases of poorly differentiated squamous carcinoma that were deeply invasive. Here the characteristic pattern consisted of finger-like projections of invasive tumor, often cut across in such away as to appear in the sections as isolated masses or nests, which in all but a very few cases lay within one or two low power microscopic fields of the main tumor (27 per cent of 252 cases) (fig. 7).

FIG
25484

TABLE 4. *Modes of local invasion and maximum penetration by primary tumor. Stage C was also reached by lymphatic metastasis alone in 8 cases and by isolated nests alone in 2 cases*

Type of Tumor	Stage A			Stage B_1			Stage B_2			Stage C		
	Solid mass	Strands and nests	With lymphatics	Solid mass	Strands and nests	With lymphatics	Solid mass	Strands and nests	With lymphatics	Solid mass	Strands and nests	With lymphatics
Well diff. trans	11											
Mod. diff. trans	13			10			4	(1 with nest at C)		8		
Poorly diff. trans	8			4			5	1	2	11	3	5
Mod. diff. sq				3			7		1	12	4	2
Poorly diff. sq	8		1	2	1 (1 with nest at C)	6	10	4	9	31	44	47
Undiff				1			2		2	15	10	10
Anaplastic								1		6		2
Adeno				1			1			3		
Total	40	0	1	21	1	6	29	6	14	86	61	66

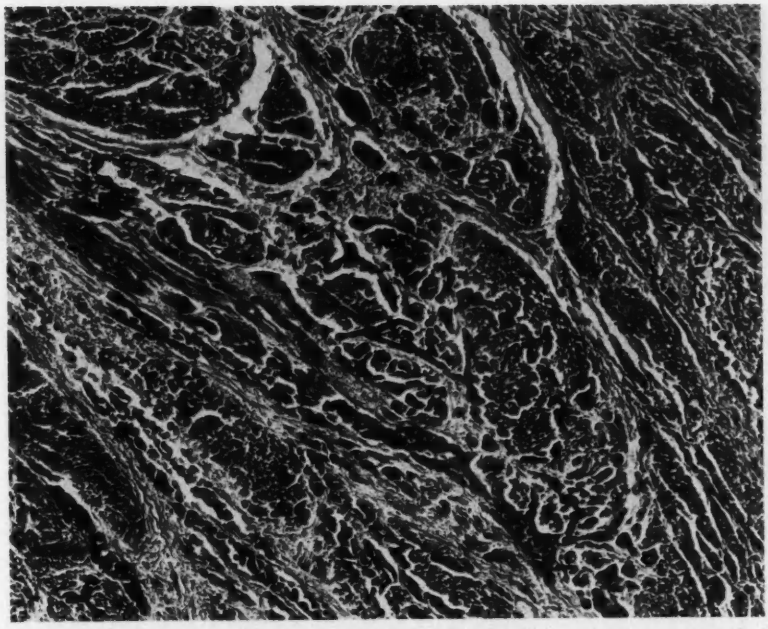


FIG. 5. Poorly differentiated squamous carcinoma with finger-like projections, stage C. Path. No. 25484. ×100.

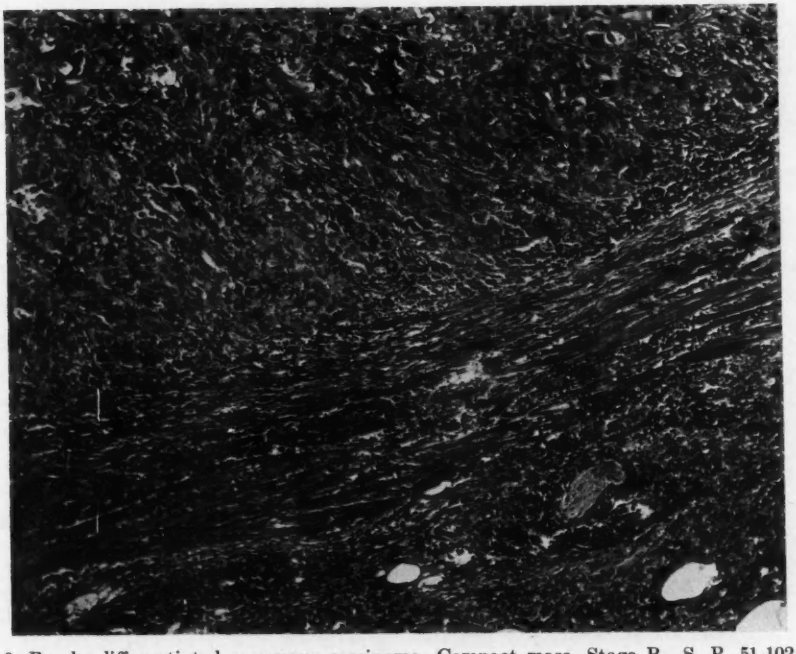


FIG. 6. Poorly differentiated squamous carcinoma. Compact mass. Stage B_2. S. P. 51-102. ×100.

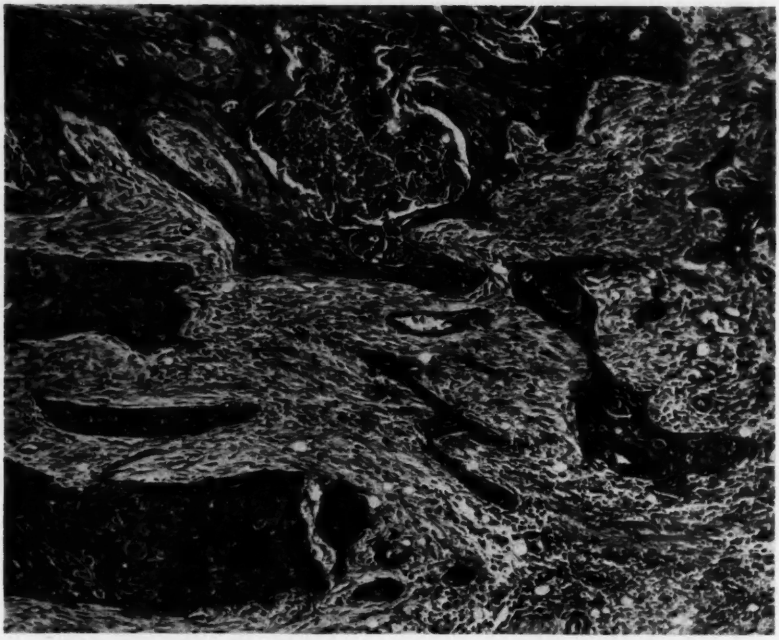


FIG. 7. Moderately differentiated squamous carcinoma. Strands and nests. Stage C. S.P. 55-4488. ×100.

The two sources of error, therefore, that make it impossible to predict from biopsy the true extent of invasion by the tumor are 1) intramural lymphatic metastasis and 2) long, slender, irregular projections that do not seem in routine sections to be connected with the overlying tumor. Since the clinical problem in staging is concerned principally with the preoperative separation of tumors in stages A and B_1 from those that are deeper, it is fortunate that these two errors occur only infrequently when the primary mass is superficial. In the present series of 63 cases in which the primary mass was in stage A or B_1, there were only three that had metastasized or extended to the fat. These were of a group of twelve poorly differentiated squamous carcinomas (25 per cent).

SUMMARY AND CONCLUSIONS

The three characteristic modes of local invasion in carcinoma of the bladder are 1) as a fairly compact mass (70 per cent), 2) as finger-like projections represented frequently as isolated masses (27 per cent), and 3) as intramural lymphatic metastases traveling in a direction more or less perpendicular to the plane of the overlying bladder mucosa (3 per cent). Miscalculation in the preoperative estimate of extent of infiltration should be infrequent. It however must be emphasized that when this error does arise it usually will be found among cases exhibiting the last two modes of invasion, especially when the tumor is a poorly differentiated squamous carcinoma.

A REPORT ON 93 ILEAL LOOP URINARY DIVERSIONS

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The ideal method of urinary diversion is still not settled. It is hoped that this paper will contribute additional information which may help to evaluate and allow comparisons between various types of urinary diversion operations.

Since 1954, ileal loop urinary diversion has been performed on 91 patients on the urologic service at the Massachusetts General Hospital. Though the use of other forms of diversion has not been abandoned, our experience has demonstrated that this method has given almost uniformly good results in surviving patients. It is, therefore, the operation of choice at present; certainly, if the upper urinary tract is abnormal. Thus far, no unexpected late complications involving the upper tract have developed. This has led to a feeling of security which contrasts rather sharply with the worry over results from other diversion operations.

It will be noted that in this series, half the cases were operated upon by the resident staff, and half by the visiting staff. Mortality and morbidity in both groups have been nearly identical. All procedures have been done without the assistance of the general surgical staff.

INDICATIONS

Ileal loop urinary diversion has been performed 47 times for palliation or cure of cancer of the bladder; 10 times for further palliation of prostatic cancer; 22 times for neurogenic vesical dysfunction with varying degrees of damage to the upper urinary tracts; 3 times for contracted bladder secondary to chronic infection; 2 times each for tuberculosis and unsatisfactory diversion by nephrostomy drainage; one each for exstrophy, ureteral obstruction due to intractable stricture, vesicovaginal fistula, urinary incontinence, and extensive recurrent rectal cancer.

It was employed twice to stabilize patients after ureterosigmoidostomy performed for cure of cancer of the bladder (2 of the 47) with complete relief of active pyelonephritis. The loop was excised and new loops constructed for 2 patients because they failed to drain properly. Poor blood supply may have been the cause of malfunction in association with stomal stenosis.

TYPES OF OPERATIONS

The method of construction and fixation of the ileal loop has not followed Bricker's technique exactly because in our early experience with the operation, it became apparent that fixation of the small bowel segment was just as important as fixation of the sigmoid in the course of ureterosigmoidostomy and that the elimination of all possibility for internal small bowel herniation was essential. Accordingly, as will be subsequently illustrated, Bricker's technique was modified by incising the posterior peritoneum in the midline at the level of the aortic bifurcation and creating a flap of peritoneum at this point. Both ureters have been delivered from the retroperitoneum at this point, the left by tunneling under the superior hemorrhoidal vessels. The closed proximal end of the ileal segment has been sutured to the tissues in the bottom of the defect thus created in the posterior peritoneum, ureteral anastomosis to the bowel done, and this whole area retroperitonealized using the peritoneal flap. This technique has allowed accurate anastomosis of the ureters to the bowel without tension, redundancy, angulation, or torsion. No instance of urinary leakage has occurred in any private case.

Simple ileal loop urinary diversion has been carried out in this fashion 47 times, was combined with simple cystectomy 10 times, and with radical cystectomy 31 times. On four occasions, because of poor ureteral function, the ureters were excised and the loop anastomosed to the renal pelves. Three were done in the presence of a single kidney and one because of bilateral ureteral dysfunction. Finally, one loop was brought through the mesentery of the sigmoid and the stoma placed in the left abdomen because of previous incision and hernia involving the right abdominal wall.

DESCRIPTION OF OPERATION

Preparation of patient. After appropriate studies indicating the need of urinary diversion, the patient is placed on a 4 day bowel preparation utilizing magnesium citrate, sulfasuxidine, low residue diet, and daily enemas. For shorter

preparation, neomycin is used. The day prior to surgery, the patient has an additional effective dose of castor oil and has the stomal site selected and scratched in place while standing, or assuming the most constant position should he not be completely ambulatory. During daily rounds, the proposed operation is fully explained to the patient, an effort made to have patient talk to a patient who has undergone the operation, the family informed of all related information, and the collection mechanism explained to all.

Operative technique. The abdominal cavity is opened through a vertical xyphoid-to-pubis incision just to the left of the midline. The viscera are palpated thoroughly for pathological changes, and a biopsy of organs or lymph nodes performed, as the situation indicates.

If a cystectomy is to be performed, this is then carried out. The ureters, isolated at the point where they cross the iliac vessels, are transected, and are drained in an extracorporeal manner through a size 8 or 10F soft Robinson type catheter, secured in the ureter with a fine silk suture.

Following abdominal exploration, or subsequent cystectomy, the ileal segment is selected, isolated, and prepared as a conduit. A portion of ileum some 6–8 inches proximal to the ileocecal valve is selected for the conduit, its blood supply identified within the mesentery by viewing against a strong light. It is important that the blood supply be provided by a single arterial branch which is identified by palpation and viewing with strong light. The mesenteric incisions are then made as far down toward the root of mesentery as possible, preserving the blood supply. The ileum is transected between Allen Kocher clamps, permitting the isolated segment to fall in a caudad direction with its mesentery after blood supply to the loop is assured. An ileoileostomy is performed using a two-layer closure, silk on the serosa-muscular layer, and catgut on the mucosal layer. The rent in the mesentery is closed with interrupted fine silk sutures, carefully avoiding mesenteric vessels. This leaves no rent in the mesentery as a potential source of internal herniation. The proximal end of the isolated segment of ileum is closed with a Parker-Kerr suture of catgut, further secured with Halsted mattress sutures of fine silk.

A transverse incision, 2 cm. in length, is made in the posterior peritoneum at the level of the aortic bifurcation. Unless the ureters have been isolated in the course of cystectomy, they are now identified in the retroperitoneal space through the peritoneum at the point where they cross the brim of the false pelvis. The right ureter is isolated, after incising the peritoneum, transected and intubated with a size 10F soft rubber Robinson catheter to permit extracorporeal drainage. The left ureter is similarly isolated and intubated, and after it is freed digitally in the retroperitoneum to the level of the lower pole of the kidney, it is brought beneath the sigmoid mesentery, and the superior sigmoid vessels in a gentle curve so as to present in the posterior peritoneal incision. It is important to have this ureter lie freely in the retroperitoneal tissues without external compression or angulation, forming a gentle arc from the renal pelvis to the site of the anastomosis.

The proximal end of the ileal segment is then secured to the retroperitoneal tissues by fine black silk sutures. The segment should lie freely, without tension, so that the left ureter may easily be anastomosed to one lateral aspect, and the right to the opposite surface of the proximal segment. Anastomosis of the ureters to the segment is made by multiple interrupted through-and-through sutures of size 5 zero chromic catgut, after trimming and "fish mouthing" the ureter to allow easy approximation with neither tension nor redundancy. The area of implantation is then retroperitonealized by suturing the flap of posterior peritoneum over the anastomoses into the bowel.

The stoma is prepared prior to any further work within the peritoneal cavity. A circular "core" of skin, fat, and external oblique fascia, roughly 4–5 cm. in diameter, is lifted out, literally, using an Allis clamp for tension. The tract is completed by manually separating the muscle fibers and incising the peritoneum to prevent angulation or baffle effect. The serosa of the segment is then secured to the peritoneum at four equally separated points by size 00 chronic catgut to fix the loop and preclude herniation about the stomal site. Using size 000 chromic catgut, the stoma is then constructed by placing 6–8 sutures about the circumference of the stoma so as to form a projecting nipple. This is accomplished by placing the sutures through the skin edge, the serosa 2–3 cm. proximal to the end, and finally through the terminal mucosa and muscularis of the loop. Any gaps are closed simply with inter-

rupted sutures between skin edge and mucosal edge. Care is taken to avoid placing any of these stomal sutures so that the blood supply of the stoma is compromised.

With the two ends of the segment secured, the free portion is then sutured to the peritoneum of the pelvis and the lateral abdominal wall by interrupted black silk sutures between the peritoneum and the antimesenteric border of the bowel segment. When completed, the segment is firmly secured and there is no potential site for internal herniation. It is important to be sure that the posterior edge of the mesentery of the segment is sutured to the posterior peritoneum for the same reason. The anterior edge of the mesentery is left free.

After inspecting the segment for viability and the bowel anastomosis for leakage and obstruction as well as viability, the abdomen is closed in layers utilizing through-and-through sutures of nylon from peritoneum up. The skin edges are approximated with Michel clips. A disposable plastic collecting bag is applied to the stoma which should be producing satisfactory amounts of urine by the time of the closure. When desirable to have the stoma on the left side of the abdomen, the ileal conduit is placed beneath the sigmoid and brought out in the previously selected stomal site in the left lower quadrant.

After operation, the patient remains on constant gastric suction and parenteral fluids until effective bowel peristalsis returns. A permanent type of collecting bag is fitted to the stoma as soon as possible to preclude skin irritation. Early ambulation is encouraged. Skin clips are removed within six days and through-and-through sutures in 10 days. If, during this time, the patient has mastered the care of the bag, he is ready for discharge. If not capable in 10 days, he remains for an additional period until either he or a member of the family has been properly instructed in the care of the bag.

After experience with several various types of collection appliances, we have found the most satisfactory system yet devised to be produced by the Torbot Mfg. Co. of Providence, Rhode Island. That bag consists of a concave plastic ring which has a roughened surface on the convex or skin side, and a custom-made hole, specifically measured for the stoma. On the concave side, a rubber collecting bag is readily attached, and it is on this side that two hooks are placed to permit an elastic belt to hold the collecting ring in place over the stoma using a satisfactory skin cement. Of all these bags so tested, this has proven to be the most satisfactory with the fewest complications and patient's complaints.

MORTALITY AND COMPLICATIONS

The mortality and morbidity figures have been admittedly too high. There have been 13 deaths (14 per cent), and 32 instances of complications, including patients who have died. Six deaths occurred on the private service with 15 complications, and 7 deaths on the house side with 17 complications.

The causes of death are given in table 1. Bronchopneumonia developed in 6 cases of which two were staphylococcal and could not be controlled. Two patients had fatal pulmonary emboli. One case of peritonitis followed an unsuspected high small bowel perforation thought secondary to trauma from retractors at the time of surgery. One death resulted from rupture of a myocardial abscess that developed in an old myocardial infarct. One patient had an exsanguinating hemorrhage from a duodenal ulcer. One death each from coronary thrombosis and malnutrition associated with sepsis was recorded.

In retrospect, the cases of pulmonary emboli, gastrointestinal hemorrhage, myocardial infarct and coronary thrombosis are unavoidable. It is unlikely that small bowel injury will occur again as the result of trauma at the time of operation. Infection will always be a serious problem, especially in older debilitated patients with neoplastic disease. It should be mentioned that 12 patients had extensive malignancy, and the

TABLE 1. *Postoperative deaths*

Total (6 private, 7 service)	13
Causes	
Bronchopneumonia	4
Staphylococcal pneumonia	2
Pulmonary embolus	2
Gastrointestinal hemorrhage	1
Peritonitis 2° perforated ileum	1
Wound sepsis c̄ rupture of myocardial abscess	1
Malnutrition c̄ sepsis	1
Coronary thrombosis	1
	13

TABLE 2. *Complications*

Private cases	15 c̄ 6 fatalities
Service cases	17 c̄ 7 fatalities
	32 13

Types of complications	
A) Early, postoperative	
Bronchopneumonia (staphylococcal 2)	6
Intestinal obstruction	3
Wound sepsis	4
c̄ Rupture of myocardial abscess	1
Stomal problems	3
Retroperitoneal abscess	2
Pulmonary embolus	2
Acute pyelonephrosis 2° ureteral obstruction (inspissated pus)	1
Peritonitis 2° perforated ileum	1
Pelvic hematoma	1
Coronary thrombosis	1
B) Late, after discharge	
Stomal problems	4
Intestinal obstruction	2
Acute pyelonephritis 2° ureteral obstruction (metastatic tumor, ureteral calculus)	2
Malfunctioning loop	1
Electrolyte imbalance 2° chronic pyelonephritis	1
Dehydration	1

thirteenth patient was 70 with severe diabetes mellitus and marked cirrhosis of the liver. The average patient age was 68. It is probable that the death rate could have been reduced appreciably through a more discriminating selection of patient, but considering that over 25 per cent in the series were more than 68 years of age, criteria are difficult to establish except in retrospect. At the time of surgery, all patients were considered in fair to good condition, and no undue risks were taken.

The complications have been considered as early; that is, immediate in the hospital; and later. The early complications are listed in table 2, A. Bronchopneumonia occurred 6 times, two of which were uncontrolled staphylococcal infections. All died. Four wounds were grossly infected, and one patient who had no demonstrable wound sepsis suffered a rupture of a myocardial abscess within an old infarct site with fatal results. Three patients had intestinal obstruction, relieved successfully by surgery. In another three infection or slough of terminal bowel developed and required later revision. Two house patients had urine leaks at the site of ureterointestinal anastomosis and retroperitoneal abscesses developed that required drainage. Two fatal pulmonary emboli occurred. Individual patients had acute pyonephrosis secondary to ureteral obstruction from inspissated pus, peritonitis secondary to perforated ileum, pelvic hematoma, and coronary thrombosis. In summary, 12 patients had nonfatal, early complications and 13 fatal complications.

Wound sepsis, retroperitoneal abscesses, pelvic hematoma, and peritonitis secondary to small bowel perforation are errors directly attributable to technique and are avoidable. It is likely that intestinal obstructions will occasionally occur after any type of major intra-abdominal surgery, but careful attention to technical details will tend to prevent this. The stomal problems arose early in the series and have not developed since specific measures have been taken for preoperative selection of stomal site and development of a better technique for stomal formation.

There were 11 long term complications encountered (table 2, *B*). Four stomal problems led the list and were corrected. Two cases of intestinal obstruction were relieved surgically, one due to adhesions in the loop area and the other by fixation of bowel by recurrent tumor. Two cases of acute pyelonephritis secondary to ureteral obstruction, one from metastatic tumor and the other ureteral calculus, were successfully operated on; the first patient lived another six months before expiring from his primary disease, while the second has been well after nephro-ureterectomy. A malfunctioning loop in a 2-year-old child secondary to stomal stenosis was replaced by another ileal segment which has functioned well. A 50-year-old patient who had ureterostomy drainage of a solitary kidney for some 18 years reentered the hospital 1 month after operation in severe hyperchloremic acidosis. Despite intensive therapy, the patient expired and at autopsy, the kidney was found to have extensive acute and chronic pyelonephritis with abscess formation. In this case there is reason to believe that ureteral peristalsis was absent or very ineffectual, and that the loop should have been attached to the renal pelvis. Finally, one patient entered the hospital 6 weeks after operation, dehydrated and moribund.

After receiving 3 liters of dextrose and water, he rapidly improved and was discharged within a week, convinced of the necessity of adequate daily fluid intake which he had voluntarily limited.

RESULTS

In considering the results of this procedure, it has successfully diverted the urinary stream in 78 cases. Sixty-five cases have been followed a sufficient length of time, six months or over, to be reasonably sure of the result. Intravenous pyelograms on these patients have been reviewed. Forty-two were normal before and after surgery. Nineteen showed impairment of abnormality of the upper tract before operation with appreciable improvement after surgery. There were four similar cases unimproved after operation. Cases showing marked improvement were suffering from neurogenic vesical dysfunction and provided gratifying justification for the operation. It has been our policy to obtain intravenous pyelograms before surgery and prior to discharge. These initial pyelograms have frequently demonstrated mild hydroureter, but subsequent postoperative pyelograms have been normal from 6 weeks to 3 months' time.

It has been our experience that unless the kidneys were badly infected before surgery, neither hyperchloremic acidosis nor pyelonephritis has developed. One patient who had been on ureterostomy drainage for 18 years did re-enter in severe acidosis and died. This solitary kidney had both acute and chronic pyelonephritis with multiple abscesses. Another patient, operated on at age 8, who had bilateral hydronephrosis and hydroureter secondary to congenital vesical neck obstruction, had had clinical pyelonephritis on several occasions. Here, in an early case, the ureters were tunnelled into the ileal segment and there is no free reflux or drainage demonstrable with the upper tracts unchanged from the presurgical status. Of the other 2 patients whose intravenous pyelograms showed damage both before and after ileal loop urinary diversion, one was 76 with generalized arteriosclerosis and poor renal function, and the latter has not yet had a 6 months' postoperative urogram to evaluate an immediately postoperative hydronephrosis. Aside from these, there are no instances of hyperchloremic acidosis or acute pyelonephritis in the series subsequent to surgery.

An additional point of interest in our results is the success in several unusual cases. On 4 occasions the ileal segment was anastomosed directly to the renal pelves, two to solitary kidneys and two to both kidneys. These patients have all shown improvement in their renal function. In another case, the patient had reduplication of his upper urinary tract with four separate, normal ureters, all of which were implanted into the proximal ileal segment, all of which drained well without evidence of postoperative hydronephrosis. The mobility and adaptability of this loop urinary diversion is truly amazing and its utility within the abdominal cavity and on the abdominal wall inexhaustible.

We prefer this means of diversion for several reasons. It has provided freedom from chronic pyelonephritis, hyperchloremic acidosis, as well as malodorous tubes. The upper tracts of patients operated on have, in the majority, remained normal or improved appreciably. In those cases where the diversion was performed for palliation, the added freedom from worry concerning ureteral or rectal obstruction by progression of the neoplastic disease, and the removal of the possibility of blockage of ureterosigmoidostomy drainage by extension of pelvic neoplastic disease into the rectum further our feelings of satisfaction with the operation. Finally, the patients themselves are comfortable with the result, those of all ages handling the applicance ably and completely.

SUMMARY

A series of 93 cases of the use of isolated ileal segments as means of urinary diversion in 91 patients has been presented.

There were 57 cases (61 per cent) performed for malignancy of the bladder or prostate and 23 cases (25 per cent) for neurogenic bladder dysfunction. The remaining cases were operated on for a variety of indications. The age span varied from 18 months to 85 years, with 64 cases (roughly 70 per cent) equally divided between the sixth, seventh, and eighth decade.

Types of operations used have been listed with a note in regard to 7 cases where the segment was placed other than in the usual location.

While the general technique has been well described previously, several points seem worthy of emphasis. The stomal site must be selected prior to surgery with the patient placed in the

most assumed posture, both erect and recumbent. The anastomoses should be retroperitoneal with the ureters lying freely in the retroperitoneal space without angulation. Particular care should be taken to fashion the stoma with sutures so placed as to cause an out-pouching of the distal end, thus permitting efficient and complete urine collection by means of an external device. All potential hernial sites within the abdominal cavity must be closed carefully and completely. It is not mandatory to have the stoma in the right lower quadrant, but rather at a point on the abdominal wall which provides a smooth surface for the application of the collection device disc.

Complications occurred in 32 instances. These have been discussed in some detail, emphasizing that infectious processes have occurred in 53 per cent of the total complications, either pulmonary or wound, that they are most common, and that the incidence is probably related to the debilitated state of elderly patients with malignancy. Stomal problems, amounting to 22 per cent of the total complications, arose in the early cases and have not been seen recently since a more satisfactory method of stomal construction has been devised. Thirteen deaths have been discussed in detail.

The results seemingly justified the operation, providing a free urinary drainage system without fecal contamination, or electrolyte disturbance. In the series of 65 intravenous pyelograms reviewed, 42 patients who had good drainage preoperatively showed no change after surgery; 19 who had impaired drainage before operation had visible postoperative improvement; while four who had evidence of impairment of drainage before surgery noticed no improvement after surgery.

This series would seem to confirm the fact that the use of isolated ileal segments in those cases wherein it is necessary to provide substitution for ureter, bladder, or urethra, is a satisfactory operation.

RENAL COMPLICATIONS AFTER ILEAC DIVERSION OF THE URINE IN NON-NEOPLASTIC DISORDERS

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The current popularity of ileac diversion of the urine* depends upon the assumption that it entails less risk of renal damage and hyperchloremic acidosis than other methods. This is based upon relatively brief periods of observation, especially when one considers that many years may intervene between ureterosigmoidostomy and clinical renal disease.

Ileac diversion has undeniable theoretical advantages. It is unlikely to cause hydronephrosis because it eliminates two potential causes: the low pressure in the ileac conduit is not transmitted back to the kidneys; and the simple ureterointestinal anastomosis ordinarily used is less liable to stricture formation than the tunnel type needed in ureterosigmoidostomy.

The danger of serious renal infection is smaller than in the presence of a foreign body (ureterostomy) or feces (ureterosigmoidostomy); there is little chance of spontaneous reflux of infected material except with stricture of the stoma.

Opportunities for intestinal absorption seem small since the ileum does not serve as a reservoir, and Pyrah and Raper believe that excretion through its mucosa counterbalances absorption fairly well. Ileac diversion is feasible when the anal sphincter is paralyzed.

There are obvious disadvantages. Its nature predisposes to immediate complications and to a substantial operative mortality; late intestinal obstruction is not rare. The external stoma invites entrance of bacteria, and stenosis is so common that we supply each patient with a dilator for its prevention.

There is more trouble with collecting devices than the uninitiated would suspect. A flush stoma requires the use of cement, to which the skin is often intolerant. A protruding stoma permits a strapped on collector which may, with careless use, compress or even erode the insensitive bowel.

* I use the term ileac diversion rather than Bricker's operation because to me, at least, the latter implies concomitant pelvic evisceration. Dennis has reminded us that Webster's unabridged dictionary gives "ileac", not "ileal" as the adjective of ileum.

Any compression or stenosis of the exit of the ileum causes a rise in pressure which is transmitted, along with resident bacteria, to the renal pelves. All collecting devices may leak; some patients never master them.

Perhaps the character of normal ileac peristalsis causes difficulty: unlike that in the ureters, it advances, stops, churns, reverses, and then starts again, so that the rate of transport is slow enough to encourage the absorption for which the ileum is designed. This may promote hyperchloremic acidosis if the kidneys are badly damaged, and may fail to drain dilated, thin walled ureters.

CLINICAL MATERIAL

We have connected segments of the ileum to the urinary tract 90 times at the University Hospital. The bladder was enlarged once, 5 ureters were replaced, and 84 ileac diversions were done. Thirty four of these were for non-neoplastic lesions, and were selected for review because they are not subject to the complications of cystectomy, nor to ureteral obstruction from recurrent cancer. The indications for the operation in this group were as follows:

Neurogenic vesical dysfunction	6
Congenital	4
Acquired	2
Congenital obstruction of vesical neck	5
Congenital ureterectasis	7
Reflux	3
Phimosis	1
Absence of abdominal muscles	1
Exstrophy	5
Post irradiation damage (bladder)	3
Malfunctioning ureterosigmoidostomy	2
Irreparable urethral strictures	1
	34

Surgical deaths	2	5.9 per cent
Late deaths	2	5.9 per cent
Longest followup		5 years

There is doubtless some overlapping among the groups classed as congenital obstruction at the vesical neck, congenital neurogenic dysfunc-

tion, and ureterectasis with atonic bladder, so that different observers would shift some patients from one group to another. In each of these cases, ileac diversion was employed only after failure followed such standard methods as cystostomy, transurethral resection, plastic revision of the vesical neck, partial cystectomy, and nephrostomy.

In one of the cases with reflux, the ureters seemed much too large and thin for the Hutch and similar operations; in the other, there was overflow incontinence after repair of complete epispadias. In the remaining cases there seemed to be nothing else to do, except in exstrophy of the bladder, where ileac diversion was intended merely as a step in its correction.

The urographic appearance of the kidneys was as follows:

Normal before operation	5
Remained same	3
Mild hydronephrosis	2
Abnormal before operation	28
Died	2
Remained same	6
Improved	11
Deteriorated	7
No followup	2
None before operation (uremia)	1
	34

Of the 5 patients with normal kidneys, four had exstrophy and one a watering pot perineum with a tightly contracted bladder from an ancient cystostomy. It is encouraging that the kidneys of 11 improved, with those of three returning practically to normal.

A cursory survey of renal function and electrolyte balance yielded the following results:

Normal before and after	14
Normal before, abnormal after	4
Abnormal before and after	12
Much worse after	6
Surgical deaths	2
No followup	2
	34

Complications of the operation were numerous.

Early, non fatal

Intestinal obstruction	2
Diaphragm at anastomosis	1
Intussusception	1
Temporary occlusion ureteral anastomosis (nephrostomy)	2
Gastric hemorrhage	1

Early, fatal

Peritonitis	2
Cause uncertain	1
Separation ureters	1

Late complications

Stenosis stoma	11
Late intestinal obstruction	2
Stones	4
Ileum	2
Kidney	2
Hyperchloremic acidosis	15
Pre and postoperative	8
Postoperative only	7
Clinical (2 fatal)	6
Dehydration with uremia	1

These, except for the electrolyte imbalances, agree pretty well with the results reported by others.

Renal failure and severe electrolyte imbalances occurred only in patients who, before operation, had pronounced renal damage from dilatation of the upper urinary tract with thin, dilated, tortuous ureters. Two have already died:

1. C. B., aged 4, number 904537. Renal dwarf with obstructed vesical neck, uremia. Cystostomy in December 1957. No improvement in hydronephrosis. Preoperative: BUN 35, CO_2 14, Cl 110, K 4.7. Ileac diversion March 26, 1958. 5/29/59: BUN 130, CO_2 6, Cl 118, K. 4.3. Died in October 1958, seven months.

2. D. W., aged 5, number 850497. Obstruction at vesical neck with uremia. Extraordinarily tortuous ureters. July 1952: Cystostomy. No benefit. November 1952: Bilateral nephrostomy. July, October 1953: Excision redundant ureters and plastic vesical neck. 1/22/57: BUN 82, CO_2 22, Cl 100, K 5.4. 1/24/57: Ileac diversion. 8/4/58: BUN 172, CO_2 8, Cl 93, K 5.3. Died in October 1958, 22 months.

Four more are in precarious condition, although not, with one exception, entirely disabled.

1. P. P., aged 11, number 850544. Obstructed vesical neck corrected successfully elsewhere in 1949. 6/25/56: BUN 38, CO_2 24, Cl. 108, K 5.1. Large hydronephroses (left functionless). Recurrent infections, no residual urine, no reflux. 9/24/58: BUN 51, CO_2 20, Cl 106, K 5.3. 9/27/57: Ileac diversion. Many episodes unexplained retention in loop. Anemia. 2/15/59: Right nephrostomy (BUN 109). 4/1/59: BUN 94, CO_2 17, Cl 98, K 3.8. Living, 18 months.

2. W. H., aged 8, number 901963. Obstruction at vesical neck. BUN 77. Cystostomy, plastic vesical neck, bilateral nephrostomy. 5/8/57: BUN 27, CO_2 21, Cl 107, K 4.4. 5/13/57: Ileac diversion. 2/24/59: BUN 58, CO_2 18, Cl 114, K 4.4. Alive, 21 months.

3. G. D., aged 8, number 757428. Congenital ureterectasis with atonic bladder. No benefit from transurethral resection, partial cystectomy. 3/12/56: BUN 43, CO_2 23, Cl 110, K 4.5. 3/15/56: Ileac diversion (incontinence). 6/15/58: BUN 32, CO_2 23, Cl 110, K 4.6. Bilateral renal calculi. 10/27/58: BUN 140, CO_2 19, Cl 83, K 6.8. 12/18/58: Left lithotomy, nephrostomy. 2/5/59: Right lithotomy, nephrostomy. 3/2/59: BUN 39, CO_2 24, Cl 109, K 4.7. Alive 24 months, bilateral nephrostomy.

4. C. P., aged 8, number 822225. Congenital ureterectasis, atonic bladder. No benefit from transurethral resection, cystostomy. Incontinent. 3/14.56: BUN 51, CO_2 13, Cl 117, K 4.5. 3/20/56: Ileac diversion. 11/29/58: BUN 254, CO_2 6, Cl 116, K 6.5. 2/17/59: BUN 64, CO_2 16, Cl 116, K 5.2. Living, 24 months.

None of these patients has much renal reserve. P. P. requires repeated tranfusions and his urea nitrogen is rising slowly. A nephrostomy has been done on his only functioning kidney with questionable benefit (six weeks). G. D. would have been saved a severe illness and further damage to her already battered kidneys if she had been hospitalized when the stones were found; her mother procrastinated until she was profoundly ill.

C. P. was admitted in coma from uremia and hyperchloremic acidosis in November while her mother was herself hospitalized so that the girl was neglected.

DISCUSSION

These operations on patients with badly damaged kidneys and ureters were done experimentally, knowing that they might fail, but feeling that there was little to lose. Why did they fail to help these six patients? So far as is known, stenosis of the ureterointestinal anastomoses was not a factor, and followup was close enough so that narrowed stomas were discovered in time to prevent lasting injury.

Causes of failure can be divided into preexisting renal and ureteral disease, and abnormal conditions established by the operation. Basic to the failure is probably renal tubular insufficiency secondary to hydronephrotic atrophy with or without complicating infection. Five of the 6 patients had hyperchloremia, and four of these had nonclinical acidosis before diversion of the urine.

Associated with this is damage to the ureters of such severity that they cannot transport urine efficiently even after removal of any resistance inherent in the intramural ureter (as postulated by Hutch). The ureters in these patients were thin, pale, greatly dilated, and tortuous, and doubtless maintained stasis after operation.

Chief among the abnormal situations created by the operation is the opportunity for absorption from the segment of bowel. One factor in this is the character of ileac peristalsis, already mentioned. That this is not as efficient as ureteral peristalsis is suggested by the failure of ileum substituted for the ureters of large hydronephroses. Fergusson and Goodwin have each reported such a failure, and we have had one in which, despite demonstrable patency of the anastomoses, a large solitary hydronephrosis required continuing drainage by nephrostomy.

Given impaired renal function and continuing ureteral stasis, it is reasonable to expect that a degree of absorption of urinary constituents which would be insignificant with a reasonably normal upper urinary tract will assume serious proportions with renal insufficiency.

Ferris and Odel and others have demonstrated the occurrence of absorption after ureterosigmoidostomy; Lapides has shown how its effects are exaggerated by renal disease. There is no doubt that the ileum absorbs many substances——this is its function. Several observers have proved that it can absorb urinary constituents. Thus Rieger and Harris found that uremia followed connection of the dog's bladder to his sigmoid by a 20 cm. segment of ileum; Davids and Bellwin had the same experience when they substituted a 35 cm. loop for the dog's bladder.

Clinically, Johnston and Rickham have cautioned against the use of ileac diversion in the presence of chronic renal insufficiency, and Goodwin has had to remove an ileac segment, substituted for a ureter, because of hyperchloremic acidosis. Swenson feels that ureteral substitution by ileum is contraindicated by chronic renal failure. My associate, Dr. J. S. Ansell, substituted ileum for the damaged ureter of a patient's only functioning (and hydronephrotic) kidney. He has a persistently elevated

serum potassium, thus opening other fields for unpleasant speculation.

I do not for one moment suggest that so valuable a procedure as ileac diversion of the urine be abandoned, but only that it should not be used in its present form in patients with chronic renal insufficiency and incompetent ureters, admitting that I do not know just where the dividing line is. It may be that lining a segment of ileum with grafts of vesical epithelium (Gilbert and associates, Martin and associates) will have some place here, but this will not solve the problem if the kidneys and ureters are badly damaged. The same may be said about Cordonnier's method of closing the urethra, excising part of the bladder, and draining it to the outside via a short ileac segment, although absorption must be less than in a conventional diversion.

SUMMARY AND CONCLUSIONS

Hyperchloremic acidosis can follow ileac diversion of the urine in some circumstances.

Pre-existing impairment of renal function and greatly dilated, tortuous, thin-walled ureters predispose to this complication, while stenosis of the stoma or of the ureterointestinal anastomoses can cause or aggravate it.

One cannot yet say what degree of renal damage contraindicates ileac urinary diversion.

Pre-existing hyperchloremic acidosis from tubular disease is probably a contraindication to this operation in its present form.

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DISCUSSION

Dr. Wyland Leadbetter (Boston, Mass.): I thought just a word of explanation in regard to our work at the General might be of some interest. Since no one is in the position to talk about the results from any operations, unless he has done the operations under discussion, what I have to say is the result of our own experience. Within the last few years our concept has been to set up a comparative series of cases of urinary diversion carried out by either ileal loop construction or conventional uretero-enterostomy. We have not abandoned any type of urinary diversion but we still are not sure just what should be done under different conditions. On the whole, we have been very pleased with our results from the ileal loop urinary diversion, and as Dr. Parkhurst has shown you, our results are better than those from uretero-enterostomy. It is obvious that the cases which Dr. Creevy has reported with such poor results represent a much more serious degree of renal disturbance than most of the cases upon which we have operated, although we have had a few cases that have fallen into that category.

We would suggest that in those patients with severe renal damage one should evaluate renal function very carefully and particularly ureteral function. The use of cinefluoroscopic techniques and perhaps pressure studies may allow us to say whether a particular patient should or should not have a conventional ileal loop type of urinary diversion. Obviously, patients with very poor kidney function and with badly decompensated ureters are not going to do well. Under these circumstances, we feel that the ureters should be abandoned and that anastomosis between the pelves of the kidneys and the ileal loop should be performed. This has been done several times with good results.

Another way of approaching this would be to try to develop a loop not covered by intestinal epithelium. This might possibly prevent the further electrolyte imbalance without impairing the delivery of urine.

We have been worried about the possibility of trouble with the skin about the ileostomy stoma and the ileum itself in patients with neurologic disease, namely because of the possibility of pressure ulcers around the stoma. This has not happened. It has been my impression that these patients have done an excellent job in caring for themselves and that ileal loop urinary diversion in the presence of neurologic disease is quite satisfactory.

Most of the difficulty has been in the construction of the loop itself or in fashioning of the stoma, as Dr. Parkhurst commented. One has to spend a good deal of effort to make a good stoma and make sure that the opening through the body wall is straight. In a few cases where loops have not worked well for us, it has been the impression that there may have been disturbance of blood supply or perhaps the mesentery was on too much tension or was twisted. I believe that one has to be very careful in fashioning a loop that the mesentery is not twisted or put on too much tension as the loop is pulled out.

Another important point is the length of a loop. One must use as short a loop as possible. Several times when we have started out with a loop that seemed to be at the right length, by the time we got ready to position the loop it seemed to lengthen considerably. I wonder if any of you have had the same experience. In these cases, we have cut down the length of the loop after it had been pulled through the body wall without interfering with the blood supply. Again, I think much of the success and, conversely, trouble with ileal loop urinary diversion will be dependent on the technique. If the operation is not done carefully, one can run into trouble.

Dr. Justin Cordonnier (St. Louis, Mo.): I warned Dr. Creevy last night that I was going to disagree with him a little bit today. I don't think his results are quite as bad as he might lead us to believe. I notice an operative mortality of less than 6 per cent. He is emphasizing the negative instead of the positive. Most of his discussion covered cases with poor results with minimal discussion of the good ones. It seemed perfectly evident that the bulk of the patients whom he showed, who were having trouble, would unquestionably have died within a very short time anyhow. Many of them had had all sorts of upper urinary tract operations. In patients with extremely advanced upper tract disease, irrespective of the type of management employed, electrolyte imbalance is inevitable in some cases and a certain percentage of them will terminate fatally.

It has been our experience with the ileal loop that in many instances we have been pleasantly

surprised with the outcome. As far as I am concerned, I know of no way to predict prior to surgery which cases are going to do well and which are going to do poorly.

There are several points I would like to mention in passing. Dr. Parkhurst has pointed out all of the difficulties with the stomas. It is my belief that the formation of a "button" adds nothing to the ultimate result. I think Dr. Leadbetter hit the point more accurately when he said it depended on the proper placing of the stoma all the way through an abdominal wall. As far as the dilatation is concerned, we routinely have the attending physician dilate the stoma at regular intervals. I think this is important.

Calculus formation has been a problem. We have had calculi form in 4 children. This is well out of line with the total number of cases involved, 24 or 25. I would like to show 3 cases which I think will somewhat refute the pictures that you have seen before.

(Slide) This first is a little boy who underwent ureterosigmoidostomy for exstrophy. He was admitted with a history of complete anuria for 48 hours and a bilateral nephrostomy was performed in 1955. This was followed in 2 weeks by ileal loop diversion and to your right is the ileogram taken after the ileal loop diversion had been performed. We have found in children that our tendency is to make the loop too long. This has been our tendency in adults, too, but it is more apt to happen in a child. We feel that especial attention should be paid to this point. This boy did not do well in spite of an open stoma. You could put the index finger in the stoma without any difficulty, and still he was continuously carrying 250 cc urine in the segment. We were pretty desperate in this case to know what to do. We inserted a Foley catheter, inflated the balloon, and brought it up with slight tension, and since then, he has had no trouble with electrolytes, or sepsis, and he is growing perfectly normal. This boy was operated upon in 1955, and he is going to school, and as far as one can tell, appears perfectly healthy. However, we don't mean to imply that he is cured by any manner of means.

(Slide) This is another one. This boy was a neglected case of vesical neck obstruction who had almost complete obstruction of his upper urinary tract. He was done in 1956, and he doesn't have much kidney left either. This fellow is in serious electrolyte trouble all the time. He takes sodium bicarbonate daily which is his only treatment, and he has done quite well clinically. He is not perfect, but I am quite sure if we hadn't provided urinary diversion, he would be dead now.

(Slide) The next one presents a happier outcome. This particular patient was admitted in very poor shape. The nonprotein nitrogen was 100 immediately following diversion. The nonprotein nitrogen is now normal, and he has had no electrolyte trouble in more than two years.

These cases are shown to emphasize the fact that in many instances a fair result can be obtained and the ultimate outcome is totally unpredictable.

DR. WYLAND LEADBETTER (Boston, Mass.): In children, it seems to me that one of the things that may cause atony of the segment is the fact that they are so active. Their abdominal musculature is contracted. In an adult the musculature is relaxed. I feel perhaps one of the reasons why children don't drain better is because their abdominal muscle is too tight, and they strain a lot. I think that may be the factor responsible for this trouble. It is just an idea.

DR. J. HARTWELL HARRISON (Boston, Mass.): I think that Dr. Creevy's results are tremendously impressive, as are Dr. Leadbetter's. I think Dr. Creevy has been trying to do the impossible. Certainly, we are not surprised if a patient does not have active peristalsis when he is in a debilitative state. We have worried about peristalsis in patients who are paraplegics, and yet they have obtained a good postoperative result.

With regard to the stoma, I think, certainly, Wyland has the right idea. We have excised the whole thickness of the abdominal wall 1½ inches in diameter to avoid stenosis. In one instance, I regretted excising that circular piece of peritoneum, because the patient extruded a loop of small bowel about two weeks after operation and had intestinal obstruction which had to be corrected. Now, we are not excising the peritoneum.

DR. PARKHURST: I would just like to say that we are looking forward to following up our studies with more interest. We also hope that we can report at a later time on a more extensive followup on this series.

DR. C. D. CREEVY: I concede that we are trying to find the borderline, that is, how bad does the upper urinary tract have to be to make it unwise to employ ileac diversion because of the danger of hyperchloremic acidosis and uremia? I do hope that, as Dr. Leadbetter has suggested, a better

solution may be found in the replacement of defective ureters with narrowed ileac segments lined with vesical mucosa. Possible applications of this method are limited by the availability of normal mucous membrane from the bladder.

One of our residents has a number of dogs living after ureteral replacement with narrowed ileac segments lined with vesical mucosa.

As concerns the formation of the stoma, we have always cut out a button of the abdominal wall. It has been my practice to select the distal site of division of the ileum by making an opening in the abdominal wall and then laying the intact ileum upon it. It is divided at a point which will permit it to protrude for one of two inches without tension. The more proximal division is made just over or medial to the left ureter as this segment lies in position. One wonders whether the reason that the loop sometimes appears to grow or elongate is to be found in the fact that it has to work continuously transporting the urine, whereas the normal ileum apparently has definite rest periods.

Relative to the type of stoma, we have made them both flush and protruding; we have left the mucosa alone, we have everted it and sutured it to the abdominal wall, and we have also slit the muscularis of the bowel before eversion. These variations don't seem to make a particle of difference in the incidence of stricture.

A group of my colleagues have reviewed their ileac diversions and have found stones in the upper urinary tract in 25 per cent after a relatively short period of followup.

SURGERY OF THE SOLITARY KIDNEY

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During the last decade, many advances have been made in the field of renal physiology, the treatment of renal disease and the management of renal insufficiency. These advances have been advantageous especially in an era of radical surgical and medical therapy. These therapeutic procedures may ultimately result in damage to one or both kidneys and at the same time their success depends upon preservation of renal function. Experience and further refinements in surgical techniques since Trendelenburg's[1] first surgical attempt to repair a diseased kidney have taught us how to preserve renal parenchyma in situations which might otherwise have been treated by nephrectomy. Conversely, further improvements in diagnostic methods have resulted in earlier detection of renal lesions such as tumors and unilateral renal vascular disease which may require the removal of a kidney. The solitary kidney that remains, if free of disease, functions essentially as well as both kidneys[2, 3] with a similar potential to maintain homeostasis. Stimulated by the loss of its mate, however, it undergoes compensatory hypertrophy and enlarges beyond the confines of its protective structures. It is then much more easily traumatized as well as more susceptible to the same disease that required extirpation of the contralateral kidney.

Solitary kidneys may be conveniently classified into the following three categories: congenital, acquired and the autonephrectomy group (i.e. a kidney destroyed by an intrinsic disease process). The congenital type has been known since the time of Aristotle[4] whereas the first successful nephrectomy was not performed until 1869 by Gustav Simon of Heidelberg[5]. At least four nephrectomies were performed prior to 1869 for intra-abdominal tumors;[6] the fatal outcome in each case suggests that these may have been solitary kidneys.

The incidence of congenital solitary kidney, according to Eisendrath,[7] varies between 1:400 and 1:4000, but the figure of 1:1000 patients appears to be generally acceptable.[8] The marked variation in incidence appears to be related to the fact that most authors did not differentiate between renal agenesis, aplasia and hypoplasia. These three may be grouped together for clinical purposes recognizing, however, that a hypoplastic kidney may function and maintain life for a variable period of time.

It is often mentioned that when an anomaly is noted in one organ or system, one should be aware of the possibilities of anomalies in the same or other systems. This observation can be exemplified by congenital solitary kidneys which are frequently associated with anomalies of the genitourinary system as well as the skeletal, central nervous, cardiovascular and respiratory systems. The more common anomalies are those related to the genitourinary tract. Anders[9] reported an incidence of associated urinary tract anomalies of 94 per cent in patients with a congenital solitary kidney, but the more usual figure appears to be approximately 50 per cent.

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[1] Mathé, C. P.: In History of Urology, edited by Bransford Lewis. Baltimore: Williams & Wilkins Co., 1933, vol. 1, pp. 329–343.

[2] Maluf, N. S. R., Ford, R. U. and Spurr, C. S.: Physiology of the human solitary kidney. J. Urol., **78:** 117–131, 1957.

[3] Bricker, N. S., Guild, W. R., Reardon, J. B. and Merrill, J. P.: Studies on the functional capacity of a denervated homotransplanted kidney in an identical twin with parallel observations in the donor. J. Clin. Invest., **35:** 1364–1380, 1956.

[4] Gutierrez, R.: Surgical aspects of renal agenesis. Arch. Surg., **27:** 686–735, 1933.

[5] Morris, Henry: In Hunterian Lectures for 1898: Origin and progress of renal surgery. Philadelphia: P. Blakiston Sons & Co., 1898.

[6] Mathé, C. P.: In History of Urology, edited by Bransford Lewis. Baltimore: Williams & Wilkins Co., 1933, vol. 1, pp. 293–304.

[7] Eisendrath, D. N.: Congenital solitary kidney. Ann. Surg., **79:** 206–221, 1924.

[8] Burford, C. E. and Burford, E. H.: Congenital solitary kidney. South. Med. J., **48:** 934–937, 1955.

[9] Anders, J. M.: Congenital single kidney with report of a case. The practical significance of the condition with statistics. Am. J. Med. Sc., **139:** 313–327, 1910.

These anomalies may be single or multiple, simple and of minimal clinical significance, or severe and actually jeopardize the life of the patient. The more common developmental urinary defects include duplication of the collecting system, aberrant renal vessels, renal ectopia and ureteral and urethral strictures. These abnormalities are obstructive or potentially obstructive and may produce urinary stasis thereby inviting infection and calculus formation which, if untreated, may lead to ultimate renal failure. Genital defects occur in 30 per cent[7] to 90 per cent[10] of female patients with a congenital solitary kidney with an average figure of 70 per cent;[4] these include minor anomalies of the tubes and ovaries, unicornuate uterus, bicornuate uterus with rudimentary horn and absent or rudimentary vagina, clitoris or labia.[7] In male patients the genital anomalies occur in 20 per cent[11] to 25 per cent;[10] these include cryptorchism and rudimentary or absent seminal vesicles, vasa deferentia, ejaculatory ducts, epididymides and prostate. The closely associated embryological development of the genital and urinary systems explains the high incidence of concomitant developmental defects.

The purpose of this report is to discuss the diagnosis, management and surgical problems of patients with solitary kidneys. A brief discussion of 13 illustrative cases treated surgically and followed for eighteen months or more is included.

DISCUSSION OF CASE REPORTS

Table 1 contains the significant clinical data of 13 patients with solitary kidneys requiring surgical intervention. Each patient manifested either overt or potential renal failure when admitted to the hospital. The majority of these patients were referred because the artificial kidney was available should the need for extracorporeal hemodialysis become necessary. None of the 13 patients required hemodialysis, however.

The cases cited in the accompanying table present different and unique problems in management and operative treatment. Urological developmental defects were the primary cause of the renal changes in seven of the 13 patients. The first 4 cases are similar in that each of these represent the congenital solitary kidney. Patients 1 and 2 are cases of increasing hydronephrosis with urinary tract infections, but without associated renal failure. The hydronephrosis in each was due to stenosis; the former at the ureteropelvic junction and the latter, in a double ureter with stenosis of a single ureterovesical orifice. A side-to-side anastomosis in continuity between ureter and adjacent renal pelvis[12] produced a satisfactory result in the former. In case 2 both ureters were re-implanted into the bladder and a most satisfactory result achieved as noted by the excretory urograms four months following surgery (fig. 1). Patient 3 was unique in that she was transferred from another hospital with anuria, severe abdominal pain and low blood pressure following minor blunt abdominal trauma. Surgical exploration revealed a hydronephrotic right kidney with a lacerated renal pelvis and associated retroperitoneal extravasation of urine and blood. Palpation of the left retroperitoneal area confirmed the diagnosis of a solitary kidney and nephrostomy drainage was therefore instituted after repairing the lacerated renal pelvis. Cystoscopic examination revealed two normal ureteral orifices, but ureteral catheterization and contrast studies showed the left ureter to terminate abruptly at the level of the third lumbar vertebra. There was no mechanical obstruction in the right ureter. The patient's blood urea nitrogen stabilized at 25–30 mg. per cent, and it was therefore elected to maintain nephrostomy drainage and re-evaluate her renal status at a later date with the view towards a definitive surgical procedure to eliminate the need for a nephrostomy tube. The patient in case 4 manifested the stigmata of advanced renal disease in a congenital solitary kidney; i.e., pyelonephritis, calculus formation and azotemia. Combined medical therapy by replacing the sodium losses and surgical removal of the calculi resulted in improvement of renal function, acidosis and general sense of well-being even though azotemia persisted. It is to be pointed out that these 4 patients are classified loosely as "congenital solitary kidneys"; only surgical exploration can conclusively differentiate between renal agenesis, aplasia and hypoplasia.

Case 5 represents the complications of a renal anomaly. Initially a nephrectomy was performed for a ruptured hydronephrotic kidney secondary

[10] Collins, D. C.: Congenital unilateral renal agenesis. Ann. Surg., **95:** 715–726, 1932.

[11] Campbell, M. F.: Congenital unilateral absence of one kidney: Unilateral renal agenesis. Ann. Surg., **88:** 1039–1044, 1928.

[12] von Lichtenberg, A.: Plastic surgery of the renal pelvis and ureter. J. A. M. A., **93:** 1706–1708, 1929.

TABLE 1. *Patients with a solitary kidney requiring surgery*

Patient	Previous Surgery	Sol. Kidney Pathology	Sol. Kidney Surg.
(1) Congenital 8 yrs. female E. A.	None	Hydronephrosis due to U-P stenosis	Pelvioureteroplasty; temporary pyelostomy
(2) Congenital 9 yrs. female C. B.	None	Hydronephrosis and hydroureter; double ureter with stenosis of ureterovesical orifice	Reimplantation of double ureters into bladder
(3) Congenital 13 yrs. female C. S.	None	Hydronephrosis; traumatic rupture of renal pelvis	Nephrostomy; repair of lacerated renal pelvis
(4) Congenital 50 yrs. male P. D.	None	Staghorn calculus; chronic pyelonephritis; chronic azotemia	Pyelonephrolithotomy; temporary nephrostomy
(5) Acquired 30 yrs. male A. R.	1) Rt. nephrectomy age 12; 2) lt. pyelolithotomy and pyeloplasty age 14	U-P junction stricture; chronic pyelonephritis; pyonephrosis	Pelvioureteroplasty; pyelolithotomy; pyelostomy for 2 mos.
(6) Acquired 54 yrs. male L. W.	1) Rt. nephrectomy age 34; 2) lt. nephrostomy 24 hrs. after ligation of aberrant vessels age 47	1) Lt. nephrostomy; 2) ureteropelvic stenosis; 3) chronic pyelonephritis	Reimplantation of ureter to renal pelvis
(7) Acquired 70 yrs. male H. H.	Lt. nephrectomy, reasons unknown;	Anuria 2° nonopaque calculi in renal pelvis	Pyelolithotomy
(8) Acquired 59 yrs. female F. C.	lt. nephrectomy age 57	Anuria 2° uric acid calculi in renal pelvis	Pyelolithotomy
(9) Autonephrectomy 50 yrs. female L. B.	None	1) Rt. nonfunctioning kidney with staghorn calculus; 2) lt. nephrolithiasis	1) Rt. nephrectomy; 2) lt. pyelonephrolithotomy
(10) Acquired 46 yrs. male W. R.	Lt. nephrectomy for renal cell ca.	Multiple tumor nodules	Kidney perfused with actinomycin-D via renal artery and vein
(11) Acquired 42 yrs. female H. M.	Rt. nephrectomy age 24	Lt. hydronephrosis 2° U-P stenosis	1) Pyelostomy; 2) pyeloplasty
(12) Autonephrectomy 33 yrs. female J. H.	None	1) Renal tubular acidosis; 2) nonfunctioning lt. kidney 2° calculi in U-P junction for 6 yrs.; 3) lower ⅓ rt. ureter packed with calculi	1) Rt. ureterolithotomy and intubated ureterostomy; 2) rt. permanent pyelostomy 3 mos. later
(13) Acquired 65 yrs. female	Lt. nephrectomy reasons unknown	1) Embolus in renal artery; 2) complete infarction of upper pole of kidney	1) Embolectomy of renal artery; 2) partial nephrectomy

to congenital stenosis at the ureteropelvic junction. Similar changes in the remaining kidney eventually led to infection, calculus formation and azotemia. A side-to-side anastomosis of the ureter to the dependent portion of the adjacent renal pelvis, pyelolithotomy and 2 months of pyelostomy drainage resulted in improved emptying of the renal pelvis. The patient is now

FIG. 1. Case 2. Double ureters with ureterovesical obstruction. *A*, before surgery; *B*, 4 months following reimplantation of ureters into bladder.

asymptomatic, although his blood urea nitrogen remains at 30 mg. per cent 24 months after operation.

Aberrant vessels to the lower pole of the kidney are often associated with stenosis of the ureteroplevic junction.[13] Case 6 illustrates the bilaterality of this entity requiring nephrectomy on one side and a nephrostomy of the remaining kidney 13 years later. This patient was referred because of recurrent attacks of pyelonephritis and emotional disturbances, both related to the 7 years of nephrostomy drainage. Re-implantation of the ureter into the renal pelvis was successful, and excretory urograms 2, 4 and 12 months after removal of the nephrostomy tube showed marked improvement in renal function (fig. 2). It is interesting to note that even after 7 years of urinary diversion restoration of continuity of the urinary tract presented no difficulty in micturition.

Cases 7 and 8 are those of anuria in a solitary kidney secondary to calculi impacted in the ureteropelvic junction. A nephrectomy had been performed previously in each case; in the former for unknown reasons, and in the latter for a staghorn calculus in a nonfunctioning kidney. Each patient was uremic (blood urea nitrogen of 160 and 232 mg./100 cc respectively) and demonstrated radiolucent calculi by contrast studies. The insertion of ureteral catheters relieved the obstructions, and the blood chemistry determinations reverted to normal. The contrast studies were performed utilizing the ureteral catheters which were draining the kidneys. The two 1.0 cm. calculi in case 7 were demonstrated by contrast studies with the patient in the upright and Trendelenburg positions. Calculi assume a dependent position during this procedure in contradistinction to artifactual air bubbles (fig. 3). The histological appearance of the calculi in case 7 was "amorphous matter and cellular debris" whereas the calculi in case 8 were composed of uric acid. A pyelolithotomy was performed in each patient, and they have been asymptomatic with normal blood chemistry determinations for 3 years.

Patient 9 is an example of an autonephrectomy secondary to a staghorn calculus (fig. 4). This kidney showed no function by excretory urography nor was there urine production or

[13] Herbut, P. A.: Urological Pathology. Philadelphia: Lea & Febiger, 1952, vol. 1, p. 377.

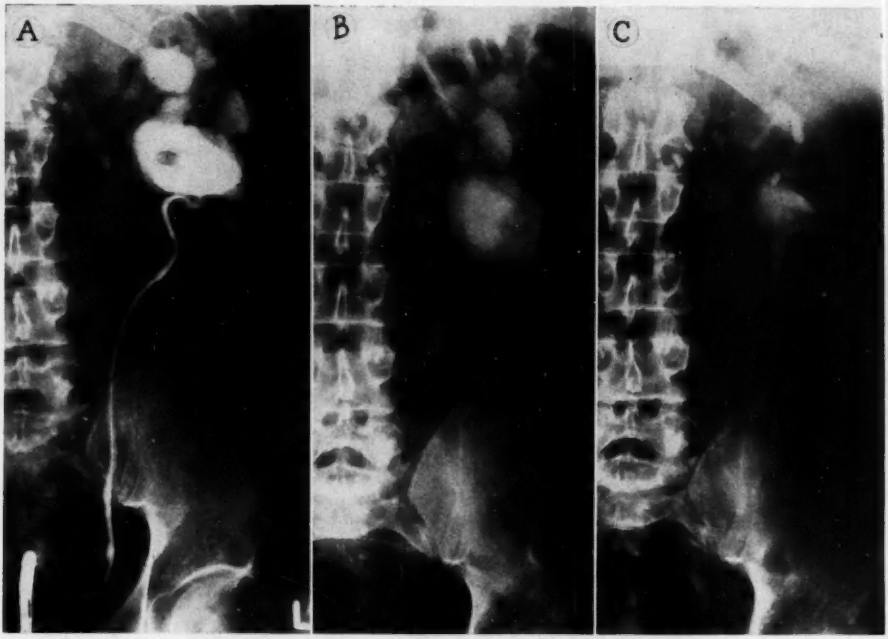

FIG. 2. Case 6. Ureteropelvic stenosis and aberrant renal vessels; nephrostomy for 7 years. *A*, preoperative contrast studies. *B*, excretory urogram 2 months following reimplantation of ureter into renal pelvis. *C*, excretory urogram 4 months postoperatively.

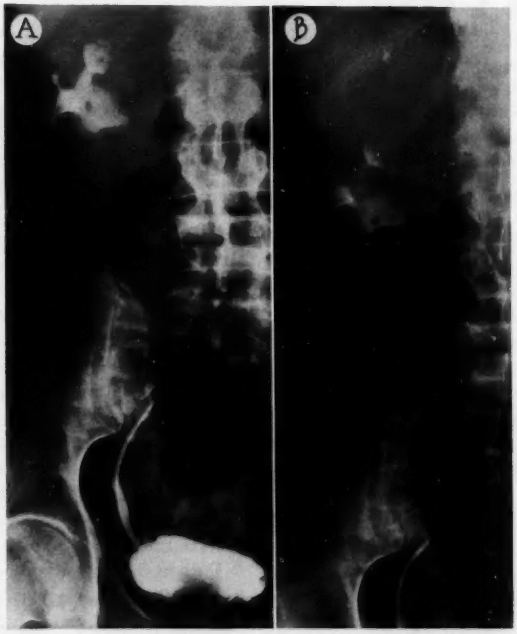

FIG. 3. Case 7. Elusive radiolucent calculi in renal pelvis demonstrated by retrograde contrast studies. *A*, Trendelenburg position; *B*, upright position.

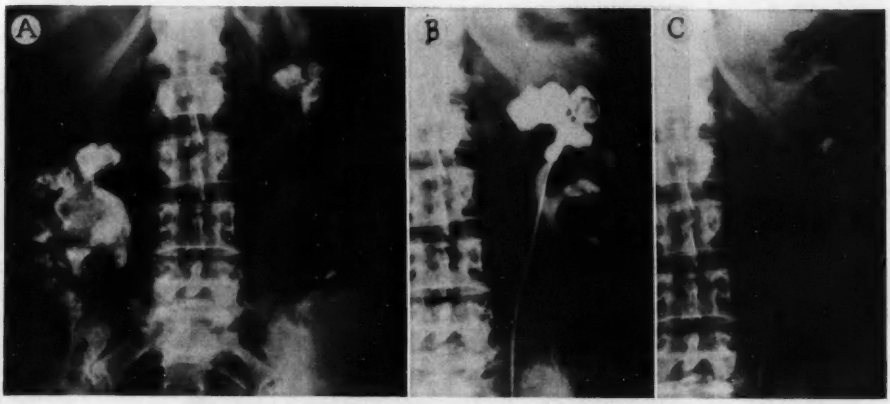

FIG. 4. Case 9. Right autonephrectomy (staghorn calculus) and left nephrolithiasis. *A*, preoperative plain film; *B*, 2 months following right nephrectomy and left pyelonephrolithotomy; *C*, 4 years postoperatively.

indigo carmine excretion when a ureteral catheter was inserted. Recurrent pyelonephritis and calculus formation in the opposite kidney necessitated removal of the infected nonfunctioning kidney and pyelonephrolithotomy of the remaining kidney. Since her surgery 4 years ago, she has had recurrent episodes of pyelonephritis without further calculus formation, but this has caused some diminution in renal function, as indicated by the blood urea nitrogen of 22 mg./100 cc.

Case 10 illustrates an heroic attempt to treat renal cell carcinoma in a solitary kidney. A left nephrectomy was performed in 1956 for a similar tumor. Two years later hematuria developed, but when anuria occurred the patient was transferred from his local hospital. An indwelling ureteral catheter relieved the obstruction from blood clots in the renal pelvis and the blood urea nitrogen rapidly fell to within a normal range. Pyelograms suggested a solitary tumor, but surgical exploration revealed multiple tumor nodules obviating any possibility of performing a partial nephrectomy. The kidney was then perfused with actinomycin-D[14, 15] through a renal arterial cannula and the fluid aspirated from the renal vein by means of a venous cannula; a minimal amount of actinomycin-D entered the general circulation by this method. A permanent pyelostomy was performed, and the patient did exceedingly well for 9 months until he abruptly became progressively azotemic and expired. Postmortem examination revealed the kidney to be almost completely replaced by tumor.

Case 11 once again illustrates the prevalence of additional anomalies when a congenital defect exists. This 42-year-old woman was found to have a hydronephrotic hypoplastic kidney which was surgically removed in 1940. In 1958 she experienced left flank pain, and urological investigation revealed a hydronephrotic left kidney containing 600 cc urine. Infection followed ureteral catheterization which required pyelostomy drainage for 2 weeks. Intrinsic stenosis of the ureteropelvic junction was found at the time the pyeloplasty was performed; this was corrected by a side-to-side anastomosis between ureter and the dependent portion of the renal pelvis with the continuity of the ureter remaining uninterrupted. A ureteral splint was left in place for 10 days. Prior to removal of the tube, a pyelogram made through the pyelostomy showed prompt appearance of the contrast material in the bladder (fig. 5).

Renal tubular acidosis is one of the less common causes of renal calculi. This congenital renal tubular defect[16, 17] is characterized by an in-

[14] Moore, G. E., DiPaolo, J. A. and Kondo, T.: The chemotherapeutic effects and complications of actinomycin-D in patients with advanced cancer. Cancer, **11**: 1204–1214, 1958.

[15] Farber, S., Toch, R., Sears, E. M. and Pinkel, D.: Advances in chemotherapy of cancer in man. Advances in Cancer Res., **4**: 1–71, 1956.

[16] Mudge, G. H.: Clinical patterns of tubular dysfunction. Am. J. Med., **24**: 785–804, 1958.

[17] Shreiner, G. E., Smith, L. H. and Kyle, L. H.: Renal hyperchloremic acidosis. Am. J. Med., **15**: 122–129, 1953.

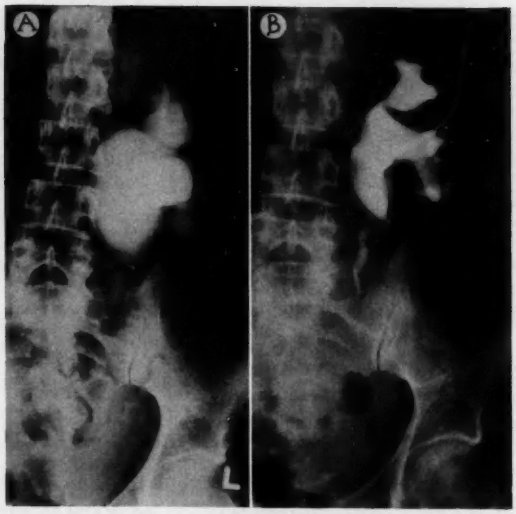

FIG. 5. Case 11. Intrinsic stenosis of the ureteropelvic junction with hydronephrotic kidney containing 600 cc urine. *A*, preoperative retrograde contrast study; *B*, pyelostomy pyelogram 2 weeks following side-to-side anastomosis between ureter and renal pelvis.

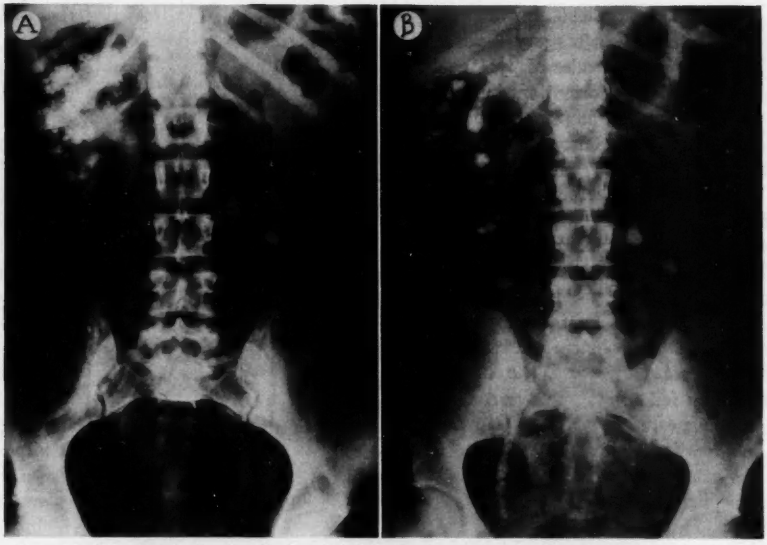

FIG. 6. Case 12. Renal tubular acidosis with bilateral renal calculi and nonfunctioning left kidney *A*, excretory urogram shows right nephrolithiasis with partial obstruction due to ureteral calculi. *B*, 1 week later following a motor trip. Calculi have fallen and impacted lower half of right ureter.

ability of the kidney to excrete acid urine. This may lead to hyperchloremic acidosis, renal calculi, potassium deficiency and nephrocalcinosis. The patient listed as case 12 was referred with an 8-year history of the passage of urinary calculi, bilateral renal calculi (fig. 6) and a known hydronephrotic nonfunctioning left kidney present for at least six years. At the time of hospitalization the lower third of the patient's right ureter was impacted with innumerable

small calculi. It was not possible to pass a catheter beyond these calculi and therefore a ureterolithotomy was performed with the establishment of an in situ intubated ureterostomy. Her postoperative course was complicated by severe hypokalemic acidosis requiring the administration of rather massive doses of potassium, sodium and calcium. Three months later a permanent pyelostomy was performed due to the recurrence of calculi and difficulty in keeping the ureterostomy free of calculi and encrustations.

A woman aged 65 years (case 13) was admitted to the hospital because of anuria 4 days in duration. A left nephrectomy had been performed elsewhere 4 years earlier for reasons unknown except for alleged infection. The patient had been well until the sudden onset of severe right flank pain followed by anuria 4 days before admission. On physical examination she was found to have mitral stenosis, auricular fibrillation, congestive heart failure and exquisite tenderness in the right flank and abdomen. Cystoscopic examination with ureteral catheterization confirmed the absence of the left kidney and no function of the right kidney. Pyelograms showed evidence of pyelonephritic scarring on the right and no ureteral obstruction. Aortography showed distortion of the right renal artery with partial obstruction and arterial spasm proximal to the branching of the renal artery where it entered the kidney. Immediate exploration of the right kidney was carried out by Drs. J. Hartwell Harrison and Chilton Crane. Multiple infarcts of the kidney with complete infarction of the upper pole of the kidney were found. The upper polar artery was completely obliterated. The renal artery was opened and an embolus removed. The renal vasculature was thoroughly irrigated through a polyethylene cannula and the artery then closed. Partial nephrectomy of the infarcted upper pole was performed. A pyelostomy tube was left in place for drainage. The kidney resumed function in 12 hours and continued to maintain good diuresis which slowly caused improvement in azotemia and restoration of electrolyte balance.

COMMENTS

The suspicion of a solitary kidney is aroused when the plain film of the abdomen reveals an absent renal shadow on one side, particularly if the visible renal shadow is enlarged and lies lower than normal. The outline of the psoas muscle on the agenetic side may be wider and less sharply defined than usual.[18] If excretory urography fails to show any excretion of contrast material on one side, cystoscopy and ureteral catheterization are indicated; a solitary kidney usually has an enlarged collecting system. A solitary kidney may be present even though two ureteral orifices are seen; the ureter contralateral to the functioning kidney ends blindly in such cases. A single ureteral orifice, however, is not pathognomonic of a solitary kidney unless it is associated with true hemiatrophy of the trigone.[18] Ureteral catheterization with instillation of contrast medium is essential to confirm the diagnosis. An ascending ureterogram utilizing a bulb type ureteral catheter should be performed in the presence of a single ureteric orifice to rule out crossed ectopia of the ureter.

Further suspicions of urinary tract anomalies should be aroused if genital malformations are found by routine pelvic and genital examination. Excretory urography is indicated in all patients with genital anomalies because of the significant number of concomitant urinary tract maldevelopments.[19] This is particularly important in female patients, as described earlier in this report.

When surgery is contemplated on a known solitary kidney, its functional status must be clearly defined preoperatively. This may be effectively assessed by such studies as blood urea nitrogen, excretory urography, phenolsulfonphthalein excretion and creatinine clearance. It is to be emphasized that when any degree of renal failure is present, the renal losses of sodium and potassium must be carefully determined preoperatively when the patient is on a normal and low sodium diet. These losses must be carefully measured and replaced in the immediate postoperative period, since the diseased kidneys, unlike "normal" kidneys, do not demonstrate the sodium conserving effect of the adrenal steroids produced under the stress conditions of surgery.

In rare situations the removal of an obstruction from the urinary tract may result in a profound

[18] Braasch, W. F. and Merricks, J. W.: Clinical and radiological data associated with congenital and acquired single kidney. Surg., Gynec. & Obst., **67**: 281–286, 1938.

[19] Felton, L. M.: Should intravenous pyelography be a routine procedure for children with cryptorchidism or hypospadias? J. Urol., **81**: 335–338, 1959.

diuresis.[20] Patient 8, for example, excreted 13.2 liters of urine in the first 24 hours following ureteral catheterization; the obstruction was due to a nonopaque calculus at the ureteropelvic junction in a solitary kidney. Postobstructive diuresis usually does not respond to pituitary extracts or desoxycorticosterone acetate (DOCA) and presents a potentially dangerous situation due to the tremendous and rapid outpouring of water and electrolytes. This condition should therefore be anticipated at the time an obstruction is removed from a solitary kidney.

The solitary kidney is subject in greater frequency to the same medical and surgical disease processes as any other kidney, but the surgical considerations differ somewhat. It is incongruous to mention the fatal hazards of removing a solitary kidney, but strangely enough this error has been committed too many times as recorded in the literature[4] and undoubtedly on many more unreported occasions. Any discussion of this nature must be prefaced by a plea for prophylaxis; i.e., to preserve kidney substance when the patient is endowed with the usual number of kidneys. Granted, there are many situations where this is quite impossible and even contraindicated, but there are also many situations where removal of calculi, partial nephrectomy, ureteral replacement by intestinal or vesical segments and vascular grafts will result in a kidney capable of satisfactorily maintaining life in the event that the other kidney is removed because of trauma, tumor or disease.

The surgery of solitary kidneys is usually technically more difficult due to the increased size of the kidney coupled with the high incidence of perinephritis. The high incidence of aberrant vessels in congenital solitary kidneys frequently makes a difficult dissection hazardous especially with regard to upper polar arteries. A minimal amount of mobilization of the kidney sufficient only to carry out the planned surgical procedure is stressed since an anomalous or diseased kidney may receive a material portion of its blood supply from both aberrant vessels and the perinephric and paranephric tissues. In addition, the less the kidney is handled, the less it will be traumatized. Conservative renal surgery is essential in order to preserve functioning nephrons. When a urinary drainage tube is required, pyelostomy is preferable to nephrostomy since there is less destruction of renal parenchyma with the former. On the other hand, nephrostomy drainage *can* be established without parenchymatous destruction if a thinned-out avascular area overlying a calyx is chosen; furthermore, it is the procedure of choice following pyeloplasties to obviate additional cicatrization in the operative area. The actual choice of a drainage tube and whether or not one is used depend entirely upon the circumstances of the individual case. Concerning pyeloplasty, it has been our practice, whenever feasible, to carry out a type of repair such that continuity of the renal pelvis and ureter will not be interrupted thereby maintaining the vascular and neuromuscular supply so essential for proper healing and function. Urinary drainage tubes, when used, should be removed as soon as practicable since they tend to perpetuate urinary infection. Prior to the removal of the tubes, however, studies must be carried out with contrast media to ascertain the dynamics of emptying of the renal pelvis and ureter. Finally, a well-organized regimen directed towards fluid and electrolyte replacement and the correction of renal and extrarenal causes of renal failure is essential especially for the success of surgery on the solitary kidney.

[20] Bricker, N. S., Shwayri, E. I., Reardon, J. B., Kellog, D., Merrill, J. P. and Holmes, J. H.: An abnormality in renal function resulting from urinary tract obstruction. Am. J. Med., **23**: 554–564, 1957.

SUMMARY

This report includes a summary of 13 patients with solitary kidneys requiring surgical treatment. The pertinent aspects of diagnosis from the clinical and roentgenographic standpoint, and a discussion of the diverse problems in pre- and postoperative management are included. The surgical technique differs somewhat when a solitary kidney is involved; the various facets of this situation are discussed.

DISCUSSION

Dr. George W. Fish (New York, N. Y.): I should like to ask a question pertaining to this very fine presentation which Dr. Meyer has given. The question is how many times can a solitary kidney be successfully operated upon?

To encourage Dr. Harrison and his colleagues, I am able to report a case of a solitary kidney from our clinic which has been successfully operated upon five times.

Dr. J. Hartwell Harrison: I am glad to hear Dr. Fish's remarks, because they are very encouraging. On account of our medical service, we see more solitary kidneys than patients with two kidneys requiring surgery.

Dr. Frank C. Hamm (Brooklyn, N. Y.): I would like to emphasize the importance of followup studies made on the solitary kidney after nephrectomy for hydronephrosis. We have found in our review of these patients that there is a significant number who develop hydronephrosis in the remaining kidney in which it was not manifest to any degree before the operation. The development of hydronephrosis in this kidney is the result of the relationship between the amount of urinary output and the caliber of ureteropelvic juncture. Naturally, the total volume of urine excreted by the remaining kidney is greater than that before nephrectomy. The minimal type of obstruction may not produce obstruction until the burden of excretion is considerably increased. This phenomenon is observed in children with diabetes insipidus. Almost all of these children have hydronephrosis which tends to subside when the condition comes under control. We have also noted in doing excretory urograms following the injection of the radiopaque substance, which is, of course, a strong diuretic, that occasionally one will find temporary distension of the renal pelvis during the diuretic phase.

Dr. Luis A. Sanjurjo (Santurce, Puerto Rico): How often have you seen anuria?

Dr. Harrison: I think about six out of 17 were anuric at the time they were admitted to the hospital.

Dr. Sanjurjo: Following surgery, how many of them develop anuria?

Dr. Harrison: We have not had persistent anuria requiring external dialysis following surgery.

Dr. Sanjurjo: It is about ten per cent? For what period of time?

Dr. Harrison: That is a function of several things—the state of renal circulation prior to surgery, and the duration of anuria prior to surgery, and the amount of diminution of ultimate potential renal reserve that has occurred prior to surgery.

Dr. Thomas E. Gibson (San Francisco, Cal.): I would like to pose a question. Is it better to maintain the continuity of the pelvis? Is it a choice of doing that or completely excising the portion of the upper ureter and reanastomosing? I can't see that there is anything to be feared or alarmed about in doing a complete excision if you want to do so.

Dr. Harrison: I would like very much to comment on that. Dr. Gibson, we do not routinely do that. We do the type of anastomosis that seems applicable to the given case. This is a left renal pelvis with the ureter coming off laterally. We have a high insertion here. This is a left renal pelvis. This patient had renal insufficiency. I was amazed to find that he had a marked degree of active peristalsis in this ureter. It seemed very logical here to do a side-to-side anastomosis. This is one application. We have had three subsequent cases with good peristalsis in the ureter in patients with one kidney, where we gained by preserving motility, and, certainly, we would tend to preserve peristalsis if we retained continuity.

Dr. Reed M. Nesbit (Ann Arbor, Mich.): About 22 years ago, I was called upon to see a little girl. She was anuric. There was a tremendous mass in one flank. It was obvious she had only one kidney, and it was hydronephrotic. I operated upon her for the purpose of performing nephrostomy, and the first thing I came down upon, when I made the small incision, was the renal pelvis, and over the pelvis was the ureter. I said that the Almighty had put this thing here and I had better utilize it, so I did. I performed lateral anastomosis between pelvis and ureter at this particular point. I brought a nephrostomy tube out through her flank to provide drainage.

That girl about ten years later was found to be emptying the pelvis entirely. At the time of operation, we took out 1200 cc urine, and seven, eight, or ten years later we found that she had no residual urine in the pelvis, so we took out the tube. She went on and became a nurse and is now a mother. She has very little hydronephrosis today.

This same procedure was carried out by Dr. Ratliff in an identical case a year ago. It was his case that brought to mind the patient concerning whom I talked to you. In his case, 1000 cc urine was in the pelvis, and he did lateral anastomosis.

FROM THE FLOOR: You didn't try to resect?

DR. NESBIT: I did nothing.

DR. HARRISON: We are not trying to decry good anastomosis from which we have gotten, perhaps, better results than in these cases. I think this, for a certain arrangement, is worth remembering.

CINEUROGRAPHY

ROBERT A. GARRETT AND EUGENE C. KLATTE

From the Departments of Urology and Radiology, Indiana University School of Medicine, Indianapolis Ind.

Cineradiography became a practical maneuver with the development of fluoroscopic image intensification described by Coltman in 1948.[1] Prior to that date, excessively large doses of x-ray were necessary to achieve motion picture images sufficiently sharp to be diagnostic. Adaptation of the motion picture camera to the fluoroscope was reported in detail by Ramsay and his co-workers[2] in the same year. Muellner,[3] studying the mechanisms of micturition, employed fluoroscopy, recording key phases in conventional static radiographs. Kjellberg, Ericsson and Rudhe,[4] in their excellent monograph, the Lower Urinary Tract in Childhood, utilized the biplane serial changer to evaluate motion. Cineradiography of the bladder and urethra was described by Benjamin[5] and by Hinman, Jr.[6] As equipment has become available, wider usage in urology has followed. Excretory urography, retrograde pyelography, antegrade urography, cystography and particularly voiding cystourethrography in all but the obese patient can be successfully visualized with this technique.

TECHNICAL FACTORS

Equipment. Five inch Westinghouse and Phillips image intensifiers were adapted to standard fluoroscopic tables. A special sling was constructed which facilitated positioning for voiding cystourethrography (fig. 1). Five millimeters of aluminum filter were used. Cineradiography was performed at 8 to 15 frames per second. The average technical factors for a 6-year-old child are 70–80 KV at 2 to 6 MA. This would deliver 1–5 roentgens per minute to the skin of the patient. The method of recording dose is a varied one. At the low exposure dose rate with diagnostic radiological equipment, the danger of the injury to the skin or other organs is negligible. It is now accepted that all radiation to the gonads is objectionable. In order to evaluate the gonadal dose with cineurography, it would seem best to compare it to the gonadal dose obtained with other accepted diagnostic radiological procedures. A papier-maché phantom of a 6-year-old child was constructed and the radiation gonadal dose measured for various diagnostic procedures. For cineurography, a 30 second exposure was made while scanning the bladder and both upper tracts. A second 30 second exposure was then made over the bladder neck with the child in a 45 degree left anterior oblique position. These gonadal dose measurements are recorded in table 1. It will be seen that the gonadal dose was less with cineurography than with accepted diagnostic radiological procedures.

All cineurographic examinations were recorded on 16 mm. Linagraph Shellburst film. While it is true that the larger film size of 35 mm. film may give a better inherent definition, the unsharpness factors of the image intensifier are such that this is difficult to perceive on projection. Film cost and processing, storage, and projection problems are significantly less with 16 mm. film.

An analyzing projector is essential for the proper interpretation of cineurography. Two units designed for this work are the perceptoscope and the Watson-Weinberg modification of the kodak analyst. Both units allow slow motion projection and prolonged single frame analysis without danger of burning the film.

This study was supported by the Riley Memorial Foundation, James Whitcomb Riley Hospital for Children, Indianapolis, Ind.

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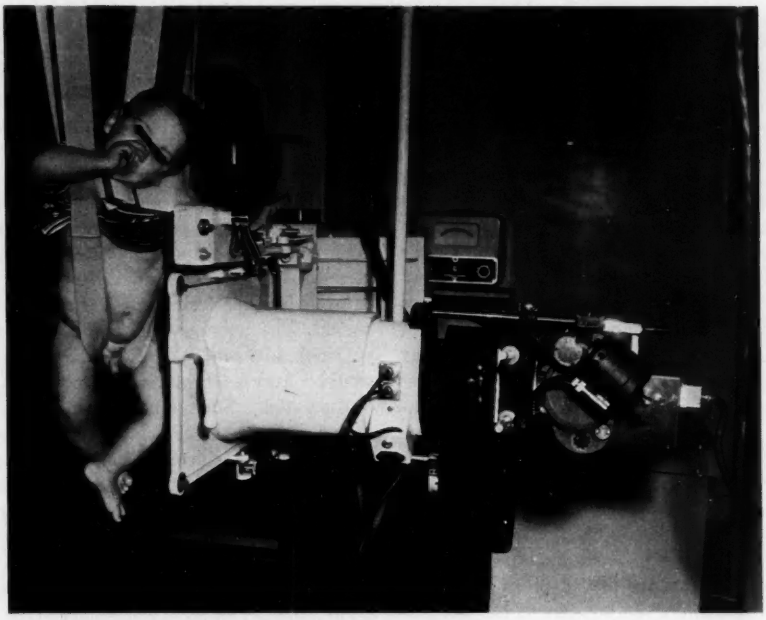

FIG. 1. Vertical sling for suspension of infants during cineurography, between fluoroscopic table on left and fluoroscopic tube with camera on right.

ADVANTAGES

There seems little doubt that, in general, motion studies of motile viscera have greater diagnostic yields than conventional static films. Not only are urine transport dynamics visualized, but by single frame study, phase positional changes are evident. Obstructive lesions may be elucidated which might otherwise be poorly appreciated. Since the use of this modality, momentary ureteral reflux undetected by conventional cystography has been seen. Hydroureter may be evaluated as to tonicity and urine transport capability (fig. 2). Ureteral calculus manipulation and, under special circumstances, ureteral catheterization might be carried out under the fluoroscopic component alone advantageously. Cineurography may yield valuable information in the incontinent patient.

DISADVANTAGES

Cost and cumbersome characteristics of the equipment are major deterrents to common practice. Both may be expected to improve in coming years. Those features notwithstanding, efforts in our departments are being directed to the adaptation of this equipment to the cystoscopic table. With proper selection of clinical material, radiation dosage should not be considered excessive for information gained.

TABLE 1. *Gonadal dose in milliroentgens (6-year-old child)*

Examination	Males	Females
Voiding cinecystourethrography (60 sec.)	180	155
Voiding cystourethrography (2 radiographs)	1100	620
Intravenous urogram	825	510
Barium enema	475	410
Lumbosacral spine	1275	790

SUMMARY

Cineurography offers an additional modality for investigation of the urinary tract. Dynamics of these motile viscera may be better evaluated than through other conventional methods. While

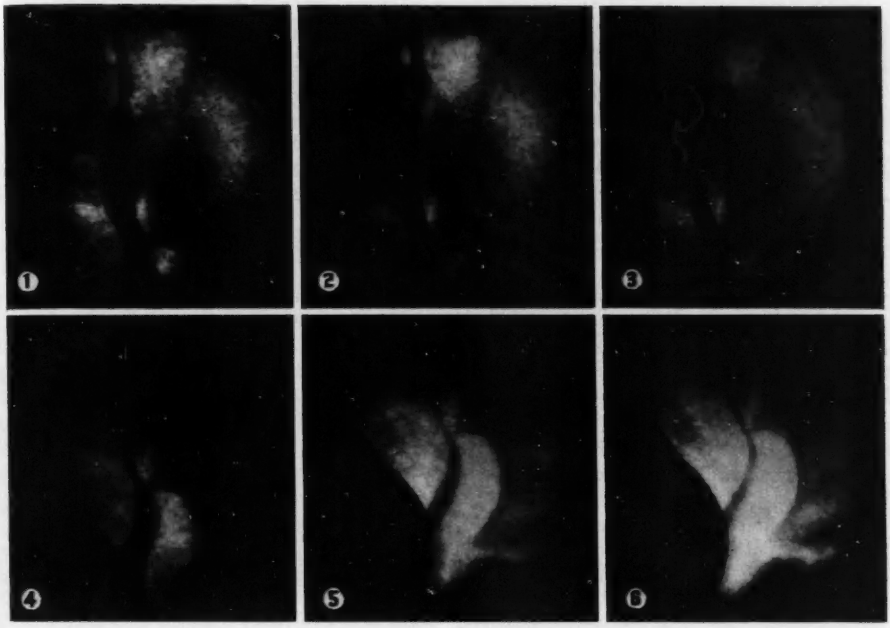

FIG. 2. Six serial frames taken from 3 second sequence of left ureteral peristalsis. Note progression of contraction wave down the lower third of ureter.

the apparatus necessary for these studies is expensive and cumbersome, improvement in these areas may be confidently expected. Advantages, disadvantages and certain technical features bearing on this technique are discussed. Radiation dosage is not considered excessive when care is taken in selecting suitable clinical material and in the proper use of the apparatus.

DISCUSSION

DR. GRAYSON CARROLL (St. Louis, Mo.): A day spent with Mr. Howard Hanley in London, in which the entire time was devoted to cineradiography, impressed me that the technique was quite practical. When I returned to St. Louis I found that all the equipment we needed was being used by the cardiac division of surgery, and that they ofttimes obtained a quick glimpse of the kidneys when observing the heart. It would appear that one of its most useful areas would be the determination of peristalsis in hydroureters in children. Cineradiography gives an excellent impression of the activity of the ureters and their ability to empty, thus making it possible to decide whether a child with marked renal damage should undergo bilateral nephrostomy or cystostomy.

We have found that merely using the fluoroscopic screen and filling the bladder with opaque solution rendered the filling and emptying of the ureters readily observable in cases where there is marked enlargement. The intensified screen is used frequently in Stockholm, Sweden, by catheterizing the femoral vein and passing a Coudé catheter into the vena cava and, under fluoroscopy, guiding it into the renal vein, then injecting the opaque solution directly into the renal vessels, thus procuring very good renograms.

FROM THE FLOOR: Dr. Garrett, how much did your whole apparatus cost?

DR. GARRETT: The cineradiographic equipment consisting of 200 MA 120 KV X-ray generator fluoroscopic table, 5 inches to 9 inches image amplifier and motor travel ciné camera is listed at current cost of approximately $15,000.00 to $30,000.00.

DR. CARROLL: It is the whole motion picture apparatus to which I was referring.

DR. GARRETT: We have two image amplifiers. The picture that you see is that of the Phillips, which is somewhat lower in cost than the Westinghouse, but without some of the Westinghouse features.

DR. CARROLL: That is what I was told.

DR. GARRETT: I am sure it is much less than the figure given you.

DR. JOHN L. EMMETT (Rochester, Minn.): Is there just an intermittent exposure?

DR. GARRETT: The Phillips equipment gives continuous exposure and Westinghouse equipment is synchronized to give intermittent exposure with less dosage. We have taken films at the rate of 15 frames per second, which is probably not necessary and which can be moved down to 8 frames. There would be a corresponding reduction in radiation dosage.

NEW DRUGS FOR TREATMENT OF GENITOURINARY TUBERCULOSIS: A COMPARISON OF EFFICACY

JOHN K. LATTIMER, GIL VASQUEZ AND HERMAN WECHSLER

From the Squier Urological Clinic, Columbia University, Presbyterian Hospital and the Research Unit for Genitourinary Tuberculosis, Kingsbridge Veterans Administration Hospital, New York, N. Y.

During the past few years several new antituberculosis drugs have become available and have been tested for efficacy at the co-operative research units for genitourinary tuberculosis at the Kingsbridge Veterans Administration Hospital and the Presbyterian Hospital in New York City. Since the duration of a course of modern chemotherapy for renal tuberculosis is of the order of 2 years, considerable time must elapse before sufficient information can be gathered concerning the efficacy of any new drug, even as a preliminary report. The purpose of this article is to discuss such information as is now available concerning several new drugs and to compare them with the established drugs now in use, both as to efficacy and toxicity. An effort will be made to clarify some of the points of debate which have arisen in connection with already established drugs, as well.

There are several new drugs. Kanamycin is one which has definite antituberculosis activity. It is probably of approximately the same order of effectiveness as streptomycin. There appears to be no crossresistance with streptomycin, so the patients who have failed on streptomycin will usually show bacteria which are still susceptible to kanamycin. The principal drawback of kanamycin is its greater ototoxicity, in that it can cause deafness, if it is given daily, within a shorter number of weeks, than streptomycin (table 1). As with streptomycin, the older the patient and the more the pre-existing eighth-nerve damage, the more severe the effects of kanamycin. On the other hand, we have been administering kanamycin to a number of patients at the rate of 1 gm. twice weekly, for the past six to nine months, without any ill effects whatsoever on the audiograms. It is our practice to combine kanamycin (1 gm. twice weekly) with conventional doses of isoniazid (100 mg. 3 times daily), and one other drug, and to give this combination for 2 years, if the patient will tolerate it. We have combined these drugs with either sodium PAS (5 gm. 3 times daily) or with thiocarbanidin, without eliciting any untoward toxic reactions as a result of the combination. Patients who have been on these combinations for approximately one year have all remained negative for M. tuberculosis in the urine during that time. These patients are still under treatment. Kanamycin is still in the early phase of being an expensive drug, as of this writing, as indeed was streptomycin when it first came out. While kanamycin would undoubtedly be more effective if given daily, the chance of toxicity fairly well prohibits its use on a daily basis over a long period of time. It is also slightly nephrotoxic, causing casts in the urine, but no frequent kidney damage, other than a transitory rise in the blood urea nitrogen in some patients with previous renal damage. The drug behaves slightly more like neomycin, in regard to its toxicity, than streptomycin. It is an effective anti-tuberculosis drug, however, even when used twice weekly, in combination with isoniazid and other drugs. The form which is effective against tuberculosis is given intramuscularly. Another form, which can be given by mouth, is not effective against tuberculosis because of its poor absorption from the intestine. It is particularly valuable in patients whose organisms have become completely resistant to streptomycin.

Cycloserine is another new antituberculosis drug which has the great advantage that it can be given by mouth. It is not as effective as streptomycin but may be of the same order of effectiveness as PAS if a sufficient dose can be tolerated by the patient. The big drawback about cycloserine is the fact that it is a convulsant drug and will cause marked cerebral stimulation and even convulsions, if too large a dose is given. The most effective dose is probably in the toxic range, necessitating the use of doses which may not be as efficacious as larger doses. A dosage of 250 mg. (1 capsule) twice daily is well tolerated by almost all patients. If the dose is increased, many

TABLE 1. *Toxicity from new drugs; 6 months followup; 78 patients with renal damage due to tuberculosis*

Thioban	13 pts.	No toxicity
Kanamycin 2 × wk	13 pts.	1 rash; No increase in albumin, casts, BUN. or hearing loss
Cycloserine	52 pts.	6 had convulsions; 11 had transient increase in casts

patients begin to feel lightheaded and eventually severely depressed, with the danger of convulsions. Such patients cannot even take their 2 capsules daily at intervals closer than 12 hours, without having the danger of convulsions. It had been hoped that the administration of pyridoxine, 50 mg. with every dose of cycloserine, might reduce the incidence of toxic reactions to an acceptable point. Unfortunately this has not proved to be true in our experience, and it has been necessary to cut back the dosage to 250 mg. twice daily, in most of our patients. Nevertheless, even at this reduced dosage, the drug does have some antituberculosis effect, apparently, and combines well with other antituberculosis drugs. Cycloserine has the distinct advantage that it can be given by mouth.

Thiocarbanidin is a new antituberculosis drug which is effective if a blood level of the drug can be achieved. It has the advantage that it can be given by mouth and is relatively nontoxic, but it has the distinct disadvantage that it is very poorly absorbed from the intestine and thus an effective blood level is very difficult to achieve with the presently available forms of the drug. Work is now in progress to improve the absorption of the drug by making it into a microsuspension in an effort to promote better absorption. Until this is achieved, this drug is of limited effectiveness for practical use. The dosage is .250 mg. 4 times daily (fig. 1).

Viomycin is another streptomycin-like drug which is not as effective as streptomycin but has roughly the same danger of toxicity for the eighth nerve, namely ataxia and possibly deafness, as does streptomycin. If viomycin is given at the rate of 2 gm. twice weekly, or 1 gm. twice weekly, however, this danger is lessened and is of about the same order of magnitude as from streptomycin. This is not a serious toxicity if life-saving treatment is required. The drug can be given at the rate of 1 gm. daily or 2 gm. twice weekly, or even 1 gm. twice weekly, if it is necessary to

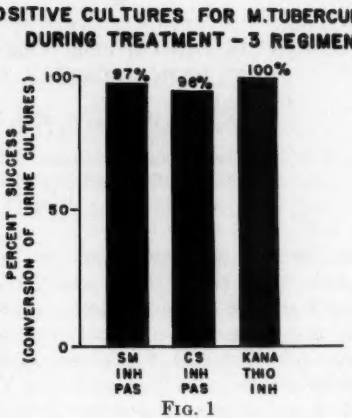

FIG. 1

reduce the dose further because of marginal toxic symptoms. This drug will also combine well with other drugs and is very similar to streptomycin in all its properties.

Pyrizinamide is another drug, used for the chemotherapy of tuberculosis, which is fairly effective if combined with isoniazid, but to which the organisms will become resistant relatively quick, if they are not eradicated. Thus the action of the drug may be fairly short-lived and it finds its maximum usefulness in bringing about a short remission of tuberculosis which has been resistant to other drugs, while a patient is being prepared for surgery, for instance. This drug has the advantage that it can be given by mouth. It has a very strong disadvantage in the fact that it causes hepatic toxicity in many patients, with many cases of death due to acute yellow atrophy of the liver having been reported. Since there are so many other less toxic drugs available now, it would seem that this drug should have a very limited place in the treatment of renal tuberculosis and should be used only in special situations where organisms were resistant to all other drugs, and where a short term effect was required. A very close watch for hepatic toxicity must be maintained throughout its usage so that it can be discontinued immediately upon the first signs of any toxicity. Even then it may be too late to prevent severe liver damage subsequent to the stopping of the drug.

Neomycin is even more nephrotoxic than kanamycin but is distinctly effective as an antituberculosis agent. It probably will cause eighth nerve toxicity with the same frequency as kanamycin. This drug is practically never used

for the parenteral treatment of renal tuberculosis, although its use might be considered in desperate cases where the organisms are found to be resistant to all other drugs. Neomycin can be used for local instillations into the bladder in cases with tuberculous ulcerations of the bladder, but such use has the disadvantages of all topical treatments in that the exposure to the drug is too brief and the dilution by the urine too rapid to permit effective action.

Hinconstarch, iproniazid, streptovaricin, vivoniplen and the thiosemicarbasones have been observed but not considered worthy of extensive testing on the evidence available to us.

Clorpactin is a chlorine releasing irrigating solution which is beneficial for topical irrigations of bladders with tuberculous ulcerations. The instillation of a .2 per cent solution for one minute followed by the replacement of the solution with fresh solution for two or three interchanges of the drug, will bring about a beneficial effect for some tuberculous ulcerations. Too enthusiastic application of this medication may bring about severe pain and even bleeding from the bladder, however, and it must be used only up to the pain tolerance of the patient, and with some caution. Irrigations may be done every day or every other day, or every third day, according to the tolerance of the patient.

NEW FACTS ABOUT OLD DRUGS

With the passage of further time, during which our cases have been observed for possible bacteriological and symptomatic relapses, we have continued to observe that triple drug regimens appear to be slightly more efficacious than double drug regimens (fig. 2). Our "classic" regimen of streptomycin 1 gm. twice weekly, sodium PAS 5 gm. three times daily, and isoniazid 100 mg. three times daily, given for two continuous years, has continued to be the most effective regimen we have tested to date. We fully realize that this is contrary to the teachings of pulmonary tuberculosis therapists, who staunchly advocate the combination of isoniazid and PAS for one or two years, as the optimum treatment for pulmonary tuberculosis. However, the two drug regimen, isoniazid-PAS, when given to patients with renal tuberculosis, has not proved to be quite as efficacious as the triple drug regimen in any of the three series of patients which we have had the opportunity to observe closely. For that reason we continue to recommend 3 drugs as most effective, with the flexibility that kanamycin can now be substituted for streptomycin if the patient's organisms are resistant to streptomycin, and cycloserine can be substituted for any one of the other medications if the patient becomes intolerant of them. Viomycin could also be substituted for streptomycin, if necessary.

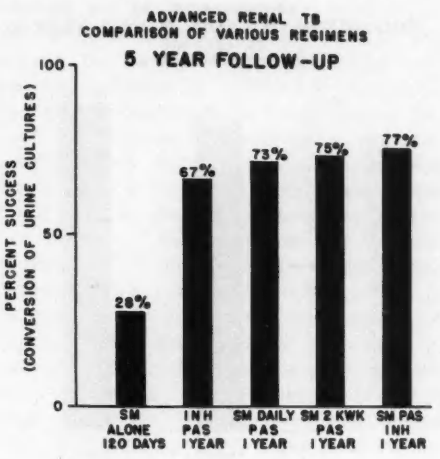

FIG. 2

Isoniazid continues to be the most effective and most easily tolerated single anti-tuberculosis agent. It is known that some patients derive less benefit from an ordinary dose of isoniazid because of their peculiar ability to acetylate this drug at an uncommonly high rate, thus rendering it inactive. This has brought about the suggestion that higher doses of isoniazid might be more effective, and we are currently engaged in testing a regimen using isoniazid 600 mg. daily (200 mg. 3 times daily) plus PAS, as against ordinary doses of isoniazid (100 mg. 3 times daily) plus PAS. It is possible that this higher dosage of isoniazid may prove to be a much more effective "two-drug" regimen, and it is well worth a trial. Toxicity from isoniazid consists of the danger of peripheral and optic neuritis. Peripheral neuritis can be extremely painful and lasts unusually long, even after the drug is stopped. Optic neuritis can bring about permanent blindness, which has been reported. As a safeguard against neuritis, all patients who are receiving isoniazid should also be receiving pyridoxin (vitamin B-6) 50 mg. twice daily, throughout the period of administration of isoniazid. This will greatly reduce the incidence of toxic neuritis from this

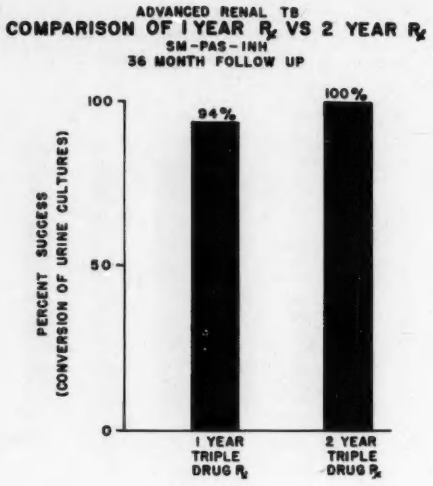

FIG. 3

drug and is a "must" in regard to any therapeutic program using isoniazid.

The duration of chemotherapy should be two continuous years. This opinion is based upon the findings of viable tubercle bacilli in the centers of caseous lesions from patients who have had only one year of triple drug treatment. While these organisms had been attenuated by the drug treatment, they were not completely killed, even though the patients had become clinically "well" and the tuberculous lesions had sealed themselves off satisfactorily. It is possible that these lesions might have gone on to sterilize themselves if sufficient time had been allowed. Two years of treatment is now our recommended regimen and we have found that preliminary results appear to show a somewhat higher rate of arrest with the two year program as compared with the one year program (fig. 3).

Daily administration of streptomycin may be slightly more effective than twice weekly administration of the drug, although our own figures do not show any advantage for the patients who received the drug daily, over the patients who received it twice weekly. If one can interpret the results obtained in pulmonary tuberculosis one would be inclined to deduce from the results of the British workers in pulmonary tuberculosis that the daily use of streptomycin is advantageous. "Regular" streptomycin is preferred by us over dihydrostreptomycin because of the greater tendency of dihydrostreptomycin to cause deafness. Dihydrostreptomycin may cause somewhat less ataxia, but may still cause this complication in patients who are elderly or susceptible to eighth nerve damage. In patients who do have eighth nerve damage already, there may be some advantage in using a mixture of dihydrostreptomycin and ordinary streptomycin, half and half, which may give less eighth nerve toxicity of all types. This contention has not yet been conclusively proven, but does seem reasonable. The objection which has been raised to the use of combinations of these drugs is that patients may become resistant or allergic to both drugs if they are used together, while if they were used singly the patient would still have the possibility of being able to use one drug or the other, should resistance or allergy develop.

Sodium PAS is decidedly easier on the gastrointestinal tract than ordinary PAS. It is necessary to increase the dose from 12 gm. (of PAS) to 15 gm. of sodium PAS (5 gm. 3 times daily) if one is to obtain an equivalent dose.

The nuisance value of having to take 10 half-gram pills of sodium PAS three times daily is considerable, and even though this preparation is fairly well tolerated, there are still some patients who have gastrointestinal bloating and discomfort as well as loose stools throughout the 2 years of treatment, much to their discomfiture. These patients are in the minority and are frequently ladies who must live at home with much leisure time to think about these symptoms. One group of manufacturers has contended that the gastrointestinal effects of PAS can be minimized by using strictly fresh preparations of the drug. They also suggest that the effectiveness of the drug may be greater when it is taken as a fresh preparation. The drug can be purchased at only slightly greater expense, in powders or tablets which yield exactly the equivalent of 12 gm. PAS acid daily. These "packettes" are sold only with an expiration date on them, and are retrieved by the company for reprocessing if the expiration date has been exceeded. Tests are now being conducted in an attempt to see if these claims are justified. Some patients do appear to accept the drug better under these conditions.

Ordinary antibacterial drugs, such as tetracycline and sulfa drugs, may have some slight suppressing effect upon the growth of M. tuberculosis. For this reason, these drugs should be withheld during the period of collection of 24-hour urine specimens for culture or guinea pig

examination for M. tuberculosis. Otherwise their bacteriostatic effect may nullify the cultures and give false negative results. The bacteriostatic effect of these drugs is apparently too weak to be of much therapeutic value, especially considering the expense of the tetracycline group of drugs.

SUMMARY

Kanamycin is effective but has somewhat greater ototoxicity than streptomycin. Kanamycin is effective against M. tuberculosis. It must be given by injection and the recommended dose is 1 gm. twice weekly with frequent audiogram checks.

Cycloserine has the great advantage that it can be given by mouth but the dosage of 250 mg. twice daily, which is all that most patients can tolerate, is probably not as effective as larger doses would be. Larger doses can be attempted to see if the patient can tolerate them. Each dose should be accompanied by pyridoxin 50 mg.

Thiocarbanidin is another antituberculosis drug which can be given by mouth and is nontoxic but is so poorly absorbed in the presently available forms that it is not sufficiently effective. Tests are now under way to devise methods of increasing the rate of absorption of this potentially good drug.

Viomycin is similar to streptomycin except that it is not quite as effective. It can be given at the rate of 2 gm. twice weekly, in combination with other drugs.

Pyrizinamide can be given by mouth and is effective for a brief time, when combined with isoniazid. Not only does drug resistance develop quickly, however, but hepatic toxicity is a serious and frequent complication, sometimes resulting in the death of the patient. For this reason this drug should be used only occasionally and in desperate situations.

Neomycin and clorpactin can be used for local irrigations of tuberculous bladder ulcerations.

Isoniazid should always be used in conjunction with pyridoxine 50 mg. twice daily, to guard against permanent and complete blindness (optic neuritis) or peripheral neuritis. Isoniazid should never be used without pyridoxin. High doses of isoniazid are now being tested, in combination with PAS, in order to help the patients who detoxify this drug at an abnormally high rate, perhaps resulting in failures of treatment. Isoniazid continues to be the best drug available, as it can be taken by mouth and is relatively nontoxic. The slight danger of ataxia from streptomycin is preferable to the slight danger from deafness due to dihydrostreptomycin. Combinations of these two drugs may be useful in patients with already damaged eighth nerve apparatus. If streptomycin can be tolerated at the rate of 1 gm. daily, the effectiveness may be slightly greater than when it is given twice weekly. However, the three drug combination of streptomycin 1 gm. twice weekly, sodium PAS 5 gm. 3 times daily and isoniazid 100 mg. 3 times daily, given for a continuous period of 2 years, is highly effective in all forms of genitourinary tuberculosis. Two years of treatment appear to be superior to 1 year of treatment.

Tetracycline drugs and sulfa drugs have some bacteriostatic effect on cultures of M. tuberculosis and their administration should thus be avoided during the collection, when one is attempting to grow M. tuberculosis from the urine. Their effectiveness is so slight as to have very little therapeutic application.

With this increasing armamentarium of effective antituberculosis drugs a triple drug combination can usually be found even for the most intolerant patient. Any of these drugs can be substituted freely for any one of the other drugs with the exception that none of the mycin drugs should be combined, lest the neurological effects be accentuated. With additional drugs to fall back upon, the objection that triple drug therapy uses up all of the therapeutically effective drugs is no longer a persuasive argument against the use of triple drug therapy on the basis that one is not "saving an ace in the hole" if one employs triple drug therapy. This has been the argument against triple drug therapy for many years, but this now appears to be fading away, thus permitting us to enjoy the possibility of greater effectiveness of the triple drug regimens over any other drug regimens tested to date.

DISCUSSION

DR. WILLIAM HERBST, JR. (Washington, D. C.): What dose of pyridoxine is advised?

DR. LATTIMER: Fifty milligrams twice a day.

PYELONEPHRITIS: IN DEFENSE OF THE URETHRAL CATHETER

GEORGE C. PRATHER AND BERNARD R. SEARS

Pyelonephritis is the most common type of renal disease. In a chronic form it is a serious menace to life and health. Recently, some physicians have accused the catheter of being responsible for the occurrence of pyelonephritis, and have inferred that the use of the catheter can have grave consequences. The urologist, whose professional life is intimately associated with the catheter and other instruments designed to explore and treat diseases of the urinary tract, probably has some opinions about these matters. The purpose of this paper is to comment on some aspects of the relationship of the catheter to pyelonephritis.

Urologists, whose experiences now cover a period of about 50 years as a specialty, have developed great respect for the possible dangers involved by or consequences following the use of urethral instruments. Those who personally employ urethral instruments rather constantly should be qualified to discuss the proper use of these instruments, provided that their point of view is sufficiently broad to include the opinions of all who are studying the many aspects of urinary tract infection. The recent reports of Beeson,[1] Hayman,[2] Jackson,[3] Jawetz,[4] Kass,[5] and others on pyelonephritis are important indeed, if properly evaluated and interpreted.

The catheter, in relation to its use in the urinary tract, may be in a similar position to the automobile in its relation to transportation of an individual or his family. Each day people are killed by or in an automobile. These sad events are in the headlines. Caution and precaution are stressed to avoid the catastrophes associated with this vehicle. Yet many people find the daily necessities and conveniences of the automobile sufficient to warrant its continued use, on the basis that the benefits are greater than the dangers—in general.

In a discussion of the catheter and its possible affiliation with pyelonephritis, we have two main topics to expound, the disease and the instrument.

PYELONEPHRITIS

Pyelonephritis has an extensive bibliography. The pathogenesis, natural history, bacteriological considerations, symptoms and treatment are fascinating aspects of this disease. We cannot add to the many fine treatises and résumés written by Beeson,[1] Bell,[6] Brewer,[7] Cabot and Crabtree,[8] Derow,[9] Hayman,[2] Helmholtz,[10] Kass,[11] Jackson,[12] Keefer,[13] Longcope,[14] Mallory,[15] Nesbit,[16] Weiss and Parker[17] and others.

There are some published statements which seem to be pertinent to the discussion at hand. Because renal infection can develop via the ascending route (intraluminary or lymphatic) as well as via the hematogenous route, Beeson[1] has

[1] Beeson, P. B.: Factors in the pathogenesis of pyelonephritis. Yale J. Biol. & Med., **28:** 81–104, 1955.

[2] Hayman, J. M. Jr.: Chronic pyelonephritis. Bull. Tufts-New Eng. M. Center, **1:** 65–71, 1955.

[3] Jackson, G. G., Dallenbach, F. D. and Kipnis, G. P.: Pyelonephritis. M. Clin. North Amer., **39:** 297–305, 1955.

[4] Jawetz, E.: Urinary tract infections. Disease of the Month, New Book Publishers, pp. 1–31 (Nov.) 1954.

[5] Kass, E. H.: Chemotherapeutic and antibiotic drugs in the management of infections of the urinary tract. Am. J. Med., **18:** 764–781, 1955.

[6] Bell, E. T.: Exudative interstitial nephritis (pyelonephritis). Surgery, **11:** 261–280, 1942.

[7] Brewer, G. E.: Hematogenous infections of the kidney. New York Med. J., **101:** 556–560, 1915.

[8] Cabot, H. and Crabtree, E. G.: Non-tuberculous renal infections. Surg. Gynec. & Obst., **23:** 495–537, 1916.

[9] Derow, H.: Management of pyelonephritis. New Eng. J. Med., **255:** 337–342, 379–384, 1956.

[10] Helmholtz, H. F. Experimental studies in urinary infections of the bacillary type. J. Urol., **31:** 173–191, 1934.

[11] Kass, E. H. and Schneiderman, L. T.: Entry of bacteria into the urinary tract of patients with inlying catheter. New Eng. J. Med., **256:** 556–557, 1957.

[12] Jackson, G. G. and Grieble, H. G.: Pathogenesis of renal infection. Arch. Int. Med., **100:** 692–700, 1957.

[13] Keefer, C.: Pyelonephritis—its natural history and course. Bull. Johns Hopkins Hosp., **100:** 107–131, 1957.

[14] Longcope, W. T. and Winkerwerder, W. L.: Clinical features of the contracted kidney due to pyelonephritis. Bull. Johns Hopkins Hosp; **53:** 255–287, 1933.

[15] Mallory, G. K., Crane, A. R. and Edwards, J. E.: Pathology of acute and healed experimental pyelonephritis. Arch. Path., **30:** 330–347, 1940.

[16] Nesbit, R. M. and Conger, K. B.: Chronic pyelonephritis. New York State J. Med., **42:** 225–232, 1942.

[17] Weiss, S. and Parker, F.: Pyelonephritis: its relation to vascular lesions and to arterial hypertension. Medicine, **18:** 221–315, 1939.

stressed bladder infection as a dangerous precursor of pyelonephritis, even though he has written that the risk of upper urinary tract infection following cystitis cannot be stated.

Bell[6] has said that the obstructive type of pyelonephritis is about 12 times as frequent as the nonobstructive type and that obstructive lesions in the urethra, prostate and bladder promote infection of the kidneys about twice as often as obstructive lesions of the ureters above the bladder. He believes that in the early stages of the disease, ascending and hematogenous pyelonephritis may be distinguished by examination of the kidneys, but that this distinction can seldom be made in the advanced stages of the disease. He writes that the majority of patients with acute pyelonephritis recover, a few die, and a few develop chronic disease. Chronicity is favored by any anomaly which prevents drainage of the kidneys.

Derow[9] concluded that mechanical factors are probably the most important factors in the genesis and development of pyelonephritis and that very little is known concerning the resistance of the kidney to infection, especially in cases of pyelonephritis in which neither an obstructive lesion nor obvious predisposing factors can be discovered.

Hayman[2] states that persistent bacterial infection in the kidneys can undoubtedly cause progressive destruction of the renal mass, although it is more difficult to attribute the development of malignant hypertension and progressive renal failure to an infection that has long since disappeared.

Birchall and Alexander[18] have said that pyelonephritis which terminates in renal insufficiency is rare compared with the general incidence of infection of the urinary tract.

Jackson, Poirer and Grieble,[19] during a study of renal biopsies, demonstrated histological evidence of pyelonephritis in 5 of 7 patients with symptoms of acute febrile urinary infection. Evidence of disease by biopsy was also present in 8 of 11 patients with a history of chronic urinary infection with intermittent acute flareups, and in 12 of 18 patients with a history of chronic urinary infection who had no flareup. The proportion of normal biopsies decreased in relation to the duration of symptoms. Four patients who had bacteriuria but who had no urinary or systemic symptoms showed a normal renal biopsy.

Keefer[13] has remarked that diabetics develop pyelonephritis four times as often as non-diabetics. One of the curious features about both acute and chronic pyelonephritis is the fact that the disease is caused most often by micro-organisms that live normally in the gastrointestinal tract.

Weiss and Parker[17] found that it was often difficult to ascertain, either from the clinical or from the morphologic evidence, whether the inflammatory or the vascular lesions were primary in people dying of uremia or the complications of hypertension. They stated that the striking discrepancy between the large number of acute cases and the considerably smaller number of chronic cases of pyelonephritis indicated that acute pyelonephritis healed in the majority of instances. If the infection persists or recurs frequently, however, pyelonephritis becomes a disease of grave prognostic significance.

During a postmortem study of over 1800 cases, Gibson[20] found that a purulent infection in the kidneys occurred in 88.9 per cent of those with some form of obstruction to urinary flow in contrast to 6 per cent without evidence of obstruction.

Jackson, Dallenbach and Kipnis,[3] in an autopsy study of cases from 1925 to 1953, reported pyelonephritis as a diagnosis in 9 per cent, although it was of major importance in contributing toward death in only 3 per cent. From 1939 on, there was a progressive decrease in the percentage of cases in which pyelonephritis was demonstrated at autopsy.

In an important autopsy study of the relation between bacteriuria and pyelonephritis, MacDonald, Levitin, Mallory and Kass[21] found that in 100 autopsies, 53 per cent had no bacteria in the bladder urine, 7 had only 10–100,000 bacteria per milliliter or urine and 40 showed more than 100,000 bacteria per milliliter of urine. Of the 40 patients with gross bacteriuria, 17 or 42 per cent showed active renal infection. They state that definite conclusions concerning the manner in which bacteriuria is related to pyelonephritis cannot be drawn from their study and that a reli-

[18] Birchall, R. and Alexander, J.: Medical aspects of pyelonephritis. Medicine, **29:** 1–28, 1950.

[19] Jackson, G. G., Poirer, K. P. and Grieble, H. G.: Concepts of pyelonephritis: Experience with renal biopsies and long term observations. Ann. Int. Med., **47:** 1165–1183, 1957.

[20] Gibson, A. G.: Pyelitis and pyelonephritis. Lancet, **2:** 903–909, 1928.

[21] MacDonald, R. A., Levitin, H., Mallory, G. K. and Kass, E. H.: Relation between pyelonephritis and bacterial counts in the urine. New Eng. J. Med., **256:** 915–922, 1957.

able clinical method for determining which of the patients with bacteriuria have renal involvement remains to be explored. It is also fair to say that they implicate the catheter as a possible or probable factor causing bacteriuria and pyelonephritis.

As early as 1915 Brewer[7] did experimental work in dogs by injecting bacteria intravenously, and demonstrated that inflammatory lesions of the kidney followed only when there was a prior man made injury to the kidney.

Mallory, Crane and Edwards[15] reached similar conclusions following an experimental study in 1940. More recently, Beeson, Rocha and Guze[22] again demonstrated that in experimental animals, pyelonephritis does not develop following introduction of coliform bacilli into the urinary passages or into the bloodstream unless the kidney has been previously obstructed or traumatized. There appears to be no explanation as to why an obstructive lesion tends to alter the ability of kidney tissue to dispose of bacteria, unless the relation between urinary obstruction and susceptibility to infection is just another example of a general phenomenon which indicates that tissues under increased hydrostatic pressure exhibit diminished resistance to pyogenic infection, as proposed by Beeson,[1] Campbell,[23] Mallory, Crane and Edwards.[15]

Cabot and Crabtree,[8] in 1916, found that organisms circulate in the blood and pass through the kidneys of some patients without producing any renal lesion and yet in other patients inflammatory lesions develop in the kidney. They stated that commonly bacteria could be present in the bladder over a long period of time without producing any lesion in the kidney.

From the above opinions of outstanding authors on the subject of pyelonephritis, one might summarize as follows. Pyelonephritis occurs much more frequently in patients who have an anatomical variation in the lower urinary tract which causes obstruction, than in patients who show no structural alteration in the urinary tract. Pyelonephritis is much more common in individuals who have diabetes or other systemic disease. Acute pyelonephritis can arise either from bacterial invasion of the kidney via the bloodstream or via ascending pathways from the bladder. Patients with acute pyelonephritis usually recover, but there are some who, because of recurrent infection, will develop chronic pyelonephritis and renal failure.

The physician has the following responsibilities in regard to any patient with urinary tract infection. He should avoid measures or procedures that might facilitate the development of pyelonephritis, such as instrumentation in the presence of acute infection. He should treat, by surgery if necessary, any anatomical variation which may contribute to recurrent infection. He should regulate systemic disease by the best methods available. He should treat the urinary infection medically in a thorough manner with frequent and sufficiently long followup observations to avoid chronic renal disease.

THE CATHETER: RELATION TO URINARY INFECTION

The second section of this paper deals with the catheter in its relation to urinary infection and thus directly or indirectly to pyelonephritis.

In past years, the definition of urinary infection by bacteriological methods has not been as simple as one might suppose. For example, does a positive qualitative culture demonstrating organisms establish a diagnosis of urinary infection? Is it normal or abnormal to have a few bacteria in the urine? Does a positive culture represent a true urinary infection, or contamination from the urethra or from the technique of the test?

At present, a quantitative report of urine cultures, rather than a qualitative report, is believed necessary to prove that there is significant urinary infection. Quantitative culture reports are standard laboratory procedure today in the study of urinary infection. Guze and Beeson[24] concluded that the use of a liquid culture medium does not yield information on the number of bacteria originally present in the urine and recommend the use of plates for quantitative reports.

Sanford, Favour, Mao and Harrison[25] have stated that a degree of bacteriuria of over 1,000

[22] Beeson, P. B., Rocha, H. and Guze, L. B.: Experimental pyelonephritis: influence of localized injury in different parts of the kidney on susceptibility to hematogenous infection. Tr. A. Am. Physicians, **70**: 12–126, 1957.

[23] Campbell, M.: Clinical Pediatric Urology. Philadelphia: W. B. Saunders Co., 1951, pp. 357–372.

[24] Guze, L. B. and Beeson, P. B.: Observations of the reliability and safety of bladder catheterization for bacteriological study of urine. New Eng. J. Med., **255**: 474–475, 1956.

[25] Sanford, J. P., Favour, C. B., Mao, F. H. and Harrison, J. H.: Evaluation of positive urine cultures. Am. J. Med., **20**: 88–93, 1956.

viable organisms/ml. of urine is required for a valid diagnosis of infection. On the basis of 250 cultures, they found that approximately 5,000 to 10,000 viable organisms/ml. had to be present before the bacteria could be seen on the stained smear of the centrifuged sediment. Jawetz[4] also agrees that numbers of bacteria in excess of 500–1,000/ml. of urine are necessary to state that there is urinary infection. MacDonald, Levitin, Mallory and Kass[21] found more than 100,000 bacteria per ml. of urine in patients with active pyelonephritis.

Quantitative cultures or microscopic demonstration of bacteria seem to be required to establish a diagnosis of active urinary tract infection. This standard or concept invalidates many of the older bacteriological studies about the incidence of urinary infection in various groups of individuals (infants, pregnant women, postoperative patients, etc.).

The next question is—how should the urine specimen be obtained? The clean voided specimen from male or female will be satisfactory if the first 20 to 30 ml. urine is not used. By this method one hopes to avoid contaminating organisms which are normally present in the urethra. This technique is easily accomplished in the male patient, and a technique for the female patient has been described by Hart and Magee.[26]

In the female patient, a catheterized specimen of urine is and has been commonly used for culture studies. Here again it is important not to include the first 20 to 30 ml. of urine if one is to avoid urethral contamination. Guze and Beeson[24] cultured the tip of the catheter after it had been inserted into the urethra of 13 female patients and obtained some bacterial growth in six. In 12 patients undergoing laparotomy they compared cultures of bladder urine obtained from the bladder by needle aspiration to catheterized specimens after operation from the same patients. In 8 patients, both samples showed no growth. In four, the aspirated specimen showed no growth while the catheterized specimen grew bacteria in fewer than 100 colonies per ml.

Monzon, Ory, Dobson, Carter and Yow[27] recently made a comparative study of urine specimens obtained by needle aspiration of the bladder, catheterization and mid-stream voided methods in 34 patients. According to table 1 in their paper, of 27 patients with sterile cultures of aspirated specimens, 7 showed minimal growth (2–54 colonies/ml.) in the catheterized specimens, and somewhat larger counts (100–400 colonies/ml.) in the mid-stream voided specimens. Of 15 patients with negative cultures of the catheterized specimen, 12 (80 per cent) showed some growth in the mid-stream voided specimens. They believe that colony counts below 100,000 bacteria per milliliter of urine represent urethral contamination.

On the basis of a quantitative concept of cultures it would appear to us that either the catheterized or mid-stream voided urine specimen is reliable to demonstrate the presence or absence of real urinary infection. However, if one were to limit culture studies on the urine to qualitative methods, there could be an 80 per cent error in using mid-stream voided samples instead of catheter specimens.

Jawetz[4] believes that in female patients, urine specimens for satisfactory culture determination must usually be obtained by catheterization.

Is there danger of introducing infection to the bladder when catheterization is used to obtain the specimen? Jackson and Grieble[12] made a study of 58 ambulatory patients who were catheterized a total of 169 times at intervals of two to four weeks. By the criterion of quantitative bacteriuria the maximum rate of infection induced by repeated intermittent catheterization in the outpatient clinic was 3 per cent. From this study they concluded that intermittent catheterization in their outpatient department does not appear to be a significant factor in the pathogenesis of pyelonephritis.

At this point one might comment on how variable circumstances can influence the reliability as well as the dangers of catheterization. It is our impression that the incidence of cystitis following catheterization is even lower in office or clinic patients than in hospital patients confined to bed. The office patient rests on an examining table which insures a proper position for adequate exposure of the introitus. Perfect light is available. The procedure is carried out by two nurses, or a doctor and a nurse, one assisting the other, and it can be done easily and aseptically.

In contrast, a hospital patient is confined to bed. It may be 10 o'clock at night and the floor is

[26] Hart, E. L. and Magee, M. J.: Collecting urine specimens. Am. J. Nursing, **57:** 1323–1324, 1957.

[27] Monzon, O. T., Ory, E. M., Dobson, H. L., Carter, E. and Yow, E. M.: A comparison of bacterial counts of the urine obtained by needle aspiration of the bladder, catheterization and midstream voided methods. New Eng. J. Med., **259:** 764–767, 1958.

shorthanded. The patient in distress is an obese woman who has not voided following surgery. The nurse comes to do her duty. She is unassisted. She gets the patient in position and places a lamp at the bedside. The heavy buttocks of the patient, showing the effects of rich American living, sink into the mattress and obscure the introitus. The nurse dons her sterile gloves and peers down at the limited and obscure operative field. Aroused by apprehension at all of this preparation, or because of discomfort the patient moves one leg and knocks the lamp to one side. With her elbow, the nurse nudges the lamp back into fairly good position as best she can and continues her work in semi-darkness. Unable to see the urethral meatus clearly, she makes several probing tries with the catheter, unavoidably contacting what now may be a contaminated area, before the urethra is found, urine flows and both patient and nurse take a deep breath—signifying relief. In this situation, the specimen may not be reliable for culture and bacteria may have been introduced into the bladder. To be both safe and reliable, the technique of catheterization demands adequate facilities and personnel.

In 1955 Beeson[1] wrote that the risk of upper urinary tract infection following cystitis had not been determined. Three years later Beeson[28] reports that infection of the bladder not infrequently results from catheterization, and that this can lead to pyelonephritis.

We believe that anyone who has used catheters during a urological lifetime knows the following statements to be true. Nontraumatic sterile catheterization, using a small catheter through a properly cleansed field, is rarely followed by urinary infection in the patient who is ambulatory and who empties the bladder efficiently. Catheterization of a bed patient in good condition and who is voiding well carries a minimal risk of infection. Repeated catheterization of the ambulatory or bed patient who is not emptying the bladder will probably be followed by at least lower urinary tract infection (cystitis), whether the inefficient voiding is caused by general disease and debility or by local anatomical disease of the urinary tract. Catheterization through an acutely infected urethra or through an obstructive urethral lesion may well produce temporary bacteriemia with resultant acute pyelonephritis. Some of the general statements regarding the dangers of urinary infection following catheterization, as stated in the recent medical literature on pyelonephritis, are definitely misleading.

One should have respect for the catheter and use it judiciously, obtaining proper urine specimens without fear of complications in some circumstances as just mentioned, while in other circumstances its possible usefulness must be weighed against the probable consequences if it is not used. Again comparing the use of the catheter to the use of the automobile, let us say that if the vehicle is operated properly amidst excellent traffic and weather conditions, travel will be completed without undue risk. Improperly operated or during hazardous traffic or weather conditions, a smashed fender or worse is likely to follow.

CATHETER FOR CONSTANT DRAINAGE

The catheter, used for constant drainage of the bladder, has been accused of contributing to urinary infection. Kass and Schneiderman[11] recently reported an interesting study on three semi-comatose patients who were on constant drainage. Several days after a strain of Serratia marcescens —a motile gram negative bacillus nonpathogenic to man, was applied to the urethral mucosa near the external meatus, bacteria of the same type were recovered in the urine draining through the catheter. They suggested that entry of the organisms into the urinary bladder was effected via the urethral fluid, composed of urine and exudate which usually forms around the catheter.

Gibson[20] reported somewhat similar observations by Thiele in 1913 in which B. mycoides applied to the anterior urethra of guinea pigs was followed by a rapid spread of the organisms along lymphatics to the capsule of the kidney, retroperitoneal glands and via the thoracic duct to the bloodstream.

Shackman and Messent[29] also studied the bacteriology of the male urethra and the bladder urine in patients who had an indwelling catheter. They found little relationship between the bacterial flora of the two sites prior to surgery. After prostatectomy there was a closer relationship, but not by any means complete.

Bacterial absorption from the urethra into the bloodstream has been known for many years.

[28] Beeson, P. B.: Case against the catheter. Am. J. Med., **24:** 1–3, 1958.

[29] Shackman, R. and Messent, D.: Effect of an indwelling catheter on the bacteriology of the male urethra and bladder. Brit. M. J., **2:** 1009–1012, 1954.

Sir Andrew Clark[30] was aware of the occasional fatal febrile prostration which occurred in elderly men with prostatic obstruction who were being cared for by intermittent catheterization. Clark introduced the term "catheter fever."

Powers,[31] in 1936, studied the febrile response following instrumentation in thirty male patients who had grossly infected urine. Three positive blood cultures were demonstrated. He concluded that transient, usually unrecognized invasion of the bloodstream may occur after instrumentation of the urinary tract, that the invading organisms may be those which are responsible for the urinary infection, and that the portal of entry is probably through minute abrasions in the urethral mucosa.

Scott[32] reported 82 cases of positive blood stream infections in urological patients. Many were temporary in character and would have been missed had there been delay in obtaining the culture of the blood. He believed that most bacteriemias in urological patients were temporary and as a rule not dangerous. In 62 per cent of the patients, the bloodstream infection followed surgery. Seventy-seven per cent of the infections were bacillary and 23 per cent coccal.

No one can have any doubt that catheterization or other instrumentation of the infected urinary system is prone to produce an acute febrile response, probably caused by bacteriemia. However, clinical experience has indicated innumerable times that chronic pyelonephritis does not necessarily follow.

Related to the foregoing remarks about the urethra as a place of septic absorption and traffic for bacteria, but in a way distinct from that concept, is the fact that most patients who are on constant drainage with an urethral catheter for more than a few days show evidence of cystitis with bacteria in the urine from the bladder. In the past, it has been common urological knowledge that even with sulfonamides or antibiotic therapy systemically and bladder irrigations locally, the bacteriuria during a period of constant drainage could not be entirely eliminated. Because many patients who may require catheter drainage as part of a urological operation enter hospitals free of urinary infection, some authors have stressed the nosocomial infections that begin during hospitalization, and they have therefore acquired a hostile attitude toward the catheter.

Orsker[33] reported culture studies from various surgical clinics near Copenhagen, the majority of patients being males who were having treatment for prostatic obstruction. He concluded that the uniformity of type distribution of urinary bacteria in hospitals was caused by cross infection. The constancy and frequency of this phenomenon were surprising.

Kirby, Corpron and Tanner[34] studied urinary infections caused by antibiotic resistant coliform bacilli and believed that these bacteria were acquired in hospitals, chiefly in patients with an indwelling catheter. Catheters and solutions were not infected, so that the exact source of the resistant coliforms and their mode of entry into the body could not be explained. Several possibilities were considered; namely, the nasopharyngeal flora of hospital personnel, multiplication of bacteria in the intestinal tract with access to the urinary tract, and contamination from mattresses and blankets to the skin and catheters and introduction of bacteria to the bladder via irrigations.

Likewise Dutton and Ralston[35] observed urinary infections in a male ward and concluded that the bacteriological findings provide strong evidence of cross infection. Cultures of catheters and cystoscopes showed no growth. Their investigation of the possible sources of cross infection showed that the ward dust and air are a permanent reservoir of species of bacteria that infect the urinary tract. The hands of nurses were suspect. Staphylococci and Streptococcus faecalis survived the routine chemical disinfection of the bottles used for urine drainage. They believed, and it is not inconceivable, that bacteria ascend along sterile tubing against the flow of urine to the bladder.

Jonsson and Erlanson[36] found that practically all of the patients operated on for prostatic ob-

[30] Clark, A.: Catheter fever. Lancet, **2:** 1075–1077, 1883.

[31] Powers, J. H.: Bacteremia following instrumentation of the infected urinary tract. New York State J. Med., **36:** 323–330, 1936.

[32] Scott, W. W.: Blood stream infections in urology. J. Urol., **21:** 527–566, 1929.

[33] Orsker, I.: Nosocomial infections with klebsiella in lesions of the urinary tract. Acta Path. et Microbiol. Scandinav., **93:** 259–271, 1952.

[34] Kirby, W. M. M., Corpron, D. O. and Tanner, D.: Urinary tract infections caused by antibiotic-resistant coliform bacilli. J. A. M. A., **162:** 1–4, 1956.

[35] Dutton, A. A. C. and Ralston, M.: Urinary tract infection in a male urological ward. Lancet, **1:** 115–119, 1957.

[36] Jonsson, G. and Erlanson, P.: Effect of chemotherapy and evaluation of sensitivity tests in vitro in surgical urinary infections. Acta chir. scandinav., **107:** 1–14, 1954.

struction or bladder tumor became infected during their stay in hospital.

MacDonald, Levitin, Mallory and Kass[21] concluded that the inlying catheter is a ready means whereby bacteriuria may be induced and we agree, but we doubt their statement that the catheter may play an important part in the development of pyelonephritis.

With acknowledgment that lower urinary tract infection during a prolonged period of catheter drainage is common, let us consider the explanation and significance of this situation.

The catheter is a foreign body. A foreign body reaction in the adjacent tissue is unavoidable. The mucosa of the urethra and bladder become congested and provide a fertile field for bacterial growth and this may be destined to continue as long as the catheter is necessary. Furthermore, in patients who require surgery involving the prostate or bladder, traumatized tissue offers an additional excellent medium for bacterial growth.

Talbot, Mahoney and Jaffee[37] recently completed a survey of 50 patients who had been on catheter drainage from one to 14 years. Although all had bacteriuria, 72 per cent showed no clinical evidence of renal disease as determined by laboratory tests and intravenous pyelography. They concluded it is not so much the indwelling catheter as the development of an obstructive lesion in the upper urinary tract that leads to significant renal infection.

The significance of bacteriuria during constant drainage of the bladder by catheter is not as horrid as some writers infer. Although every possible effort should be made toward a bacteria free urine while the catheter is in place, we believe the most important question is whether or not the urinary infection remains to plague the patient after the catheter has been removed. How long does it take for the urine to clear itself of cellular elements and bacteria following operations on the bladder and prostate in which the catheter has necessarily been used for constant drainage? A period of 3 months is not unusual. Thus, in patients who have had urological surgery one should not pass final judgment regarding induced catheter infection until 90 days after operation. In all patients who have had catheter drainage, the ultimate presence or absence of bacteriuria will depend in most instances upon whether or not the urinary system empties efficiently.

Furthermore, the incidence of acute pyelonephritis as determined by clinical diagnosis is not high during the period of catheter drainage or during the immediate post-catheter period unless the patient is debilitated from systemic disease or has obstructive uropathy. The incidence of chronic pyelonephritis on the basis of catheter induced infection must be minimal indeed. During a recent conversation with Dr. E. T. Bell,[38] author and lifetime student of renal disease, Dr. Bell made the comment that infections of the lower urinary tract were not important as an etiological factor in chronic pyelonephritis.

SUMMARY

In summary, one can say that pyelonephritis is most common in children or adults who are ill with systemic disease or in those individuals who have obstructive lesions in the urinary tract, although it does occur in patients who are in good general condition and have no structural disease of the bladder, prostate, ureters or kidneys. Chronic pyelonephritis does not commonly result from one attack of acute pyelonephritis.

The catheter, properly used, can be employed safely to obtain a specimen of urine without danger of introducing infection in patients who are voiding efficiently. The catheter, used intermittently in the debilitated patient or in those who are not voiding effectively, can lead to serious urinary tract infection.

The catheter, used for constant drainage of the bladder, is frequently accompanied by bacteriuria because of foreign body reaction and the introduction of bacteria into the bladder. The indwelling urethral catheter can be used for a long time in a patient in good general condition and with a normal upper urinary tract without undue risk of pyelonephritis.

The final estimate as to the presence or absence of urinary infection must be made at a time when the tissues involved have had time to recover from foreign body reaction or surgery.

We find no evidence to implicate the catheter as a significant factor in the cause of chronic pye-

[37] Talbot, H. S., Mahoney, E. M. and Jaffee, S. R.: The effects of prolonged urethral catheterization: persistence of normal renal structure and function. J. Urol., **81**: 138–145, 1959.

[38] Bell, E. T.: Personal verbal communication.

lonephritis. No doubt the great majority of patients who develop acute pyelonephritis have never been catheterized prior to the onset of the acute infection. It is not logical to blame the catheter as a major contributor to serious urinary tract infections (unless it has been used improperly), simply because the instrument has been employed as a diagnostic or therapeutic agent in patients with urinary tract disease.

The catheter, properly used, is one of man's best friends.

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AEROGENOSIS: A PLEA FOR CLINICAL BACTERIOLOGY

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As urologists we have come to rely on a variety of other disciplines. The chemist, the engineer, and the physicist are becoming more and more essential to us every day. In the tradition of urology however, the bacteriologist has played an important role, and there is a real danger that we are losing his help as the help of others increases.

AN EXAMPLE

A little less than a year ago one of us (H. H. Z.) was called to see a 7½-year-old child who had been investigated in the outpatient department of Babies Hospital for many years for advanced Cooley's anemia. He had had, on two occasions, severe transfusion reactions with periods of anuria for as long as two days previously, and at the time I saw him was again anuric for the third time. This was secondary to a retrograde pyelogram done to delineate the irregular solitary kidney which he possessed. His temperature was 105. An electrocardiogram showed changes compatible with hyperkalemia; the nonprotein nitrogen was rising rapidly. Blood and urine cultures revealed A. aerogenes, insensitive to all antibiotics at that time available, and although the anuria was reversed by secondary catheterization and the electrolytes restored to normal, the patient continued to have an elevation of temperature to 106 in spite of injections of intravenous furadantin and intramuscular chloromycetin which failed to stop his recurrent shaking chills. Kanamycin was added to the regimen and chloromycetin stopped, after kanamycin sensitivity was shown to be presumably effective in in vitro testing. The dose was originally started at 10 mg. per kilogram every 6 hours and was increased to 15 mg. per kilogram every 6 hours. Under the impact of the fever his hemoglobin which had previously been 8 gm. fell to 4.3 gm., and in spite of other hazards he was retransfused. For the first time his blood cultures became negative, the fever gradually subsided, and he remained afebrile for the next 9 days. At that time kanamycin was discontinued after two negative blood cultures and urine cultures had been obtained. He was shifted to oral furadantin therapy for further outpatient care. Audiometric studies showed a 30 per cent hearing loss, presumably secondary to kanamycin.

THE RISE IN RESISTANT FLORA

While there is much argument in the literature at the moment as to what constitutes genuine urinary tract infection, there can be no doubt that when faced with circumstances such as the foregoing, all will agree that infection is present in its most virulent form. As urologists accustomed to urethritis and its complications, we are often inclined to regard high temperature with less seriousness perhaps than our other medical colleagues. It must be remembered that in most instances a temperature elevation more than 102 represents real septicemia. On our service an increasing number of these are due to an extremely virulent type of A. aerogenes carrying a formidable mortality (table 1). We have in particular avoided operation, if possible, in patients shown to be chronically infected with A. aerogenes until adequate antibiotic therapy is available.

The changing bacterial flora in hospital populations originally detailed by Rhodes, and by Pierson and ourselves for Los Angeles County General Hospital in 1952, has had increasing emphasis placed on the gram-negative bacilli by Kirby and Orkin. So striking was the preponderance of gram-negative organisms not as yet exposed to chloromycetin at the Los Angeles County General Hospital in 1954 that all sensitivities were discontinued and every patient placed on chloromycetin for a trial of therapy before any detailed study was performed. Despite the short-sightedness of this point of view, results were excellent for the short interval that it took to develop resistance to chloromycetin in the hospital bacterial population.

In our experimental bacteriology laboratories here at the Squier Urological Clinic origin of A. aerogenes in our more serious chronically infected cases has been found in some instances to be from the noses and throats of the nurses and resident staff (table 2). As a result we have begun to wear

TABLE 1. *Death rates from septicemias due to urinary infections*

Organism	% Death
Escherichia coli	38
Aerobacter aerogenes	60
Salmonella	33
Bacillus proteus	56
Alkaligens faecalis	50
Pseudomonas aeruginosa	75

TABLE 2. *Origin of A. aerogenes in urinary tract infections*

Irrigating fluids	0%
Cystoscopy air	0%
Nose and throat	20%

masks in the cystoscopy room for all but the most delicate procedures, and they are removed only after the instrument has been passed.

Let me emphasize that our problem is not necessarily that A. aerogenes itself is such a serious invader, but rather that resistance to antibiotics can be unusually rapidly developed in A. aerogenes to most of the drugs available to us.

THE NATURE OF RESISTANCE

Let us for a moment review the natural history of development of resistance of bacterial organisms at which the preliminary attack was so ably made by Dr. Armitage in 1952. While he was focused on the development of resistance in vitro, we have independently developed a series of equations relating to the deveopment of resistance in vivo. It can be shown further that the susceptibility of a bacterium to a drug in vivo is directly related to the lack of contact that the bacterium has had with the host, or with this drug, and is inversely related to the square of the mutation rate (fig. 1). These equations point up the fact that there is perhaps additional therapeutic advantage to be obtained by attempting to inhibit the rate of mutation of strains in vivo, that prophylactic chemotherapy may be justified to attack the organism at a time when its invasiveness is greatest and before hostile conditions have influenced the rate of mutation, and it suggests that radiation and mutagenic agents should be avoided in the treatment of infection. Perhaps the most striking example of radiation induced invasiveness is the recent attack of "pyelonephritis"

$$S = K \frac{i}{\beta^2}$$

S = susceptibility
i = lack of contact with host and antibiotic
β = mutation rate

FIG. 1

in the light water reactor at Los Alamos where a casual gram-negative contaminant of the cooling system was induced to mutate by the high levels of radiation to the point where it could survive on acrylic resins and almost stopped the functioning of the reactor.

If one reviews the over-all picture of antibiotic vulnerability to a large number of drugs for a large number of organisms, one finds that one can arrange them in such fashion that there is considerable overlap both in groups susceptible and in adverse reactions in the host. This has suggested that there may be some common metabolic pattern both in the bacteria and in the host to explain the curious coincidence of overlap which this table represents. It is likely that the nature of these dependencies will lie in very simple substrates. Indeed, there is increasing evidence to indicate that the simpler the substrates on which a bacterium can subsist the more likely it is to be extremely resistant to most of the antibiotic and antibacterial chemicals available to us (table 3). We have accordingly focused our attention on the metabolism of the gram-negative bacilli which have been most dangerous to our patients in the last 6 years. The mortality from E. coli bacteriemias has been 38 per cent, of Aerobacters 60 per cent, and of Pseudomonas 75 per cent (table 4).

Pseudomonas remains our future enemy but local attack with hibitane and systemic attack with colymycin may change the picture.

Detailed study of a variety of simple carboxylic acids has shown the amazing versatility of our most unpleasant offenders. Taking as an example acetic acid, which has been suggested as an antibacterial irrigating material it is worthwhile noting that some strains of Proteus growing in our laboratories will thrive in up to 50 per cent glacial acetic acid. Exposure to 0.5 per cent acetic acid, the strength originally suggested, for 5 minutes fails to inhibit growth of any of the strains of E. coli, B. proteus, P. aeruginosa, A. aerogenes or staphylococci which we have. Exposure to 1 per cent acetic acid for 3½ hours successfully inhibits less than 40 per cent of the strains studied. We have had little difficulty in showing that some

TABLE 3. *Correlation of enzyme activity and drug resistance*

Organism	Urease	Citrase	Drug R.
E. coli	−	−	±
Eb. typhosa	−	−	±
Shigella	−	−	±
V. chloerae El Tor	−	−	±
B. proteus colum.	++++	+	++++
B. proteus OX 2	+	+	±
Aerobacter aerog.	++	+	++++
Klebsiella pneum.	++	+	++

TABLE 4. *Cases of aerogenosis since January 1958*

Ineffective	Curative
084973 Chloramphenicol & furadantin	Kanamycin
222565 Tetracycline & furadantin	Chloramphenicol
1389388 Sulfadiazine & chloramphenicol	Furadantin
650582 Tetracycline & furadantin	Chloramphenicol
168053 Tetracycline & sulfadiazine	Furadantin

Fatal general surgical case received sulfonamides, penicillin, chloramphenicol and furadantin, to no avail.

TABLE 5. *Progress in combating aerogenosis 1958 and 1959*

Aerobacter aerogenes septicemia
Mortality reduced—60%
Incidence increased—300%
Curative drugs
Chloramphenicol
Furadantin
Kanamycin

abnormal acids such as aconitic acid effectively block some phases of the carbohydrate cycle in these organisms and detailed studies on additional elements of the Krebs cycle are still in progress. We have already blocked some phases of the nitrogen cycle. Prominent in these studies has been the study of mercurial diuretics as inhibitors of the urease activity of some urea splitting bacteria in struvite stone prevention which will form the substance of an American Urological Association exhibit next week, and more flamboyant uses of organotin materials.

MULTIPLE COUNTER ATTACK

It is to be hoped that with better knowledge of the obligatory type of substrates better reasoning than that shown by Perrin Long for multiple antibiotic therapy may be carried out. He, as you remember, successfully proved that there were synergistic and antagonistic combinations of antibacterials without formulating the type of combinations that Dr. Jawetz has so often reiterated.

We believe that combined use of two drugs is to be avoided if one is obtaining response with a single drug, but one of us showed almost ten years ago that multiple drug therapy was effective in control but not eradication.

It is extremely important that we, as urologists, carry the banner to encourage the entry of more capable clinical bacteriologists into the field of urological bacteriology. Too often it has been shown that if a bacteriologist studies something which can be seen with a light microscope and does not need an ultracentrifuge, his chances for academic advancement are severely limited. We have problems in clinical bacteriology as challenging as any in the ultrastructure field, and it is only by intimate study of each organism in each hospital at the time of its clinical importance that we will be able to consistently defeat the inroads of the bacteria carried by serial human transfer that we encourage to mutate to become lethal to man. Often success or failure, life or death hinges on precise knowledge, accurately determined,

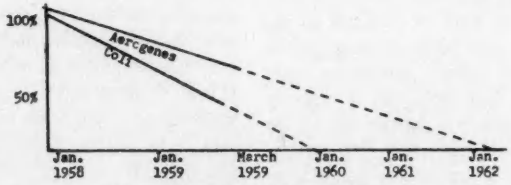

FIG. 2. Decline in sensitivity

rapidly reported, and imaginatively explored about one organism, many drugs, in one patient.

We are having success. This is manifested by the fact that the mortality from A. aerogenes septicemia in the past 12 months has been reduced from 75 per cent to 20 per cent using judicious combinations of drugs and, in two instances, the newest drug available, kanamycin (table 5). It is ominous, however, that the A. aerogenes we see now has dropped from 100 per cent sensitivity to 78 per cent sensitivity. In E. coli, the sensitivity has dropped from 100 per cent to 55 per cent (fig. 2).

Pseudomonas is still 100 per cent sensitive to colymycin in the cases to date.

It is for us as urologists to keep the field of clinical bacteriology alive so that our patients may stay alive.

DISCUSSION

Dr. Grayson Carroll (St. Louis, Mo.): This subject is close to my heart, and I am very happy to say that the observations that have been made by Dr. Zinsser and by Dr. Lattimer coincide very much with my own. While efforts are being made to stamp out staphylococci, we have almost ignored the rising importance of bacillary infections. New antibiotics such as novobiocin, vancomycin, erythromycin, and oleandomycin have been discovered to combat the Staphylococcus-resistant organism but kanamycin is the only one bacteriocidal to the bacillary resistant organism. Interestingly enough, the kanamycin will go across the line. It will affect resistant staphylococci; it will also attack resistant bacillary infections.

It is interesting to note that there are certain organisms which are likely to develop resistance early, and there are certain organisms that are not likely to. Escherichia coli develop resistance slowly. Fortunately, it is the most common organism we have in the urinary tract, and it is susceptible to practically all drugs. On the contrary, Proteus and the Pseudomonas develop resistance promptly to almost any drug to which they are exposed, and now the observation made by Dr. Lattimer places Aerobacter aerogenes in that same category.

Then, again, certain drugs develop resistance more readily than others. For example, we know that the organisms very promptly develop resistance to streptomycin, penicillin, and the cyclanes when exposed to them. On the other hand, with furadantin, methenamine, and chloromycetin, the organisms develop resistance rather slowly. That was brought out somewhat by the paper that was presented here.

Then, another comment I would like to make is that certain drugs which we are using are bacteriostatic and certain others bactericidal. Those which are bacteriostatic (chloramphenicol, tetracyclines, erythromycin, novobiocin, oleandomycin, sulfa drugs) should obviously be used for a longer period to eliminate the organism, in contrast to those which are bactericidal (penicillin, streptomycin, neomycin, vancomycin, nitrofurantoin) which can be used briefly.

Dr. David M. Davis (Philadelphia, Pa.): I should like to discuss more particularly Dr. Prather's paper and perhaps say something of the way this question appears to me, not in regard to the advance surgical infections such as those Dr. Zinsser and Dr. Lattimer have considered, but, rather, with the whole question of the onset and early stages of urinary tract infection.

I feel very strongly that the present argument arises largely from the fact that the internists have stepped into a vacuum in our knowledge. That vacuum has unfortunately been left in its empty state by physiologists and by urologists. It is a matter, I think, of great regret that it has been left that way. Let me state it in this fashion. We all know that the normal urinary tract is very resistant to infection with any kind of pathogenic bacteria. We know that obstructed urinary tracts are predisposed to infection, and furthermore, we also know of many cases in which it has been possible to relieve definite obstructions and to note that after the relief of the obstruction, the normal resistance of the urinary tract to infection oftentimes reappears and becomes permanent. However, when we use this term 'obstruction' what do we mean by it? Obstruction is actually any departure from the normal pattern of the conduction of urine through the urinary tract and to the exterior of the body. Obstruction cannot be defined until we have the exact specifications for normal conduction through the urinary tract. These specifications we still do not have. We do not know the pressures in the normal renal pelvis, nor how to measure any increase thereof, nor just how the ureteral peristaltic wave is initiated. We know more about bladder function, but, unfortunately, we do not use our knowledge as much as we should in our clinical work. The cystometer and the uroflometer should be used every day. Pyelography is unsatisfactory. It involves little more than an opinion as to whether the outline of the pelvis is normal or not and may mislead entirely as to the presence of high or normal pressures within the pelvis.

I rise here principally to make a plea that we try to fill this vacuum. At present we cannot say definitely that there is obstruction until it is in an advanced stage, nor can we ever say with absolute assurance that there is no obstruction.

When we can we will know what we are talking about.

Dr. Donald A. Charnock (Los Angeles, Cal.): I am very happy to hear this paper by Dr. Prather. Recently, I experienced a rather bad time with one of our brilliant internists, who is an expert in chemotherapeutic drugs. I innocently made the statement that I felt the female patient should be catheterized for determinations of bacterial flora. He retorted that after he had cured a patient he did not want anybody putting a catheter into that patient and stirring up the pyelonephritis again.

The unfortunate thing that I think the internist did not realize was that with the occasional patient who gets these flareups following catheterization, she has not been cured. These female patients still have the ureterotrigonitis with backpressure and residual urine which was the basis for the infection. Perhaps, they had sterilized the urine, but they had not cured their patient of the primary disease. It is because of this that they get flareups from the catheter.

I thoroughly realize that in many female patients the so-called "clean catch" can be accomplished. It is an acrobatic procedure, but it can be done. However, there are some female patients—unfortunately, the elderly patients—who are very prone to have urinary tract infections, in whom it is quite impossible to get a clean catch. They are just not built that way, and you must be as careful as you can with the catheter.

With respect to Dr. Zinsser's paper on kanamycin, we have used this drug at our Children's Hospital since it was put on the market. In Aerogenes cases, we have found it quite effective. We have had the same experience as Dr. Carroll reports that these little patients do acquire resistance to the kanamycin very early. We have not had the toxic reactions. We think it is a very fine drug. I have also been more and more impressed with the increasing number of patients who have Aerogenes in their urine.

Dr. Richard Chute (Boston, Mass.): I feel that it is my duty to issue a warning about the use of kanamycin in cases with impaired renal function—on the basis of the following case. Last summer while I was away on vacation, a 70-year old man with chronic prostatic obstruction and some degree of uremia was admitted to my service, bleeding quite profusely from his prostate. During the course of the next two or three days he received a number of blood transfusions, one of which must have been incompatible as he got acute renal tubular necrosis. This was not recognized for 24 hours (although in retrospect it could be seen that his urinary output in the 24 hours preceding operation had decreased markedly) and, since the profuse bleeding from the prostate continued, a suprapubic prostatectomy was done as an emergency for the hemorrhage. The patient reacted very poorly to the surgery, with oliguria of course (due to the already existing acute tubular necrosis), marked elevation of nonprotein nitrogen output to 150, high temperature with a positive bloodstream infection with A. aerogenes. He was given a total of 5½ gm. kanamycin over the course of 4 days. The kanamycin, plus the proper electrolyte therapy and good nursing care, cured the infection and saved his life, but on the fourth day of kanamycin therapy he had become stone deaf. That was last August—8 months ago—and he still is absolutely stone deaf, and repeated audiometric examinations have shown complete loss of hearing with no evidence of improvement with the passage of time. As soon as deafness was noticed, after 4 days of kanamycin, samples of blood were taken for analysis, which showed many times the normal therapeutic level of kanamycin.

I know of another similar case in another hospital where the administration of kanamycin to a patient with poor renal function resulted in what appears to be permanent, total deafness. It appears that, in the presence of impaired renal function, kanamycin cannot be excreted well, and the recommended dose causes a very abnormally high level to accumulate in the blood with resulting severe eighth nerve damage.

In view of these cases, I feel strongly that kanamycin should not be administered in therapeutic doses to any patient with poor renal function, unless that patient is very critically ill and the drug is prescribed as a desperate life-saving measure, with the realization that it may well result in total and permanent deafness.

Dr. Cornelius Vermeulen (Chicago, Ill.): I would like to concur heartily with Dr. Davis with regard to the vacuum of knowledge in regard to pyelonephritis. Having realized this, for the last few years our laboratory has begun an investigation of experimentally produced pyelonephritis. There are a multitude of questions that are still quite unanswered such as: how does

infection get into the kidney from the bladder? It is frequently assumed that infection rises into the kidney via the ureter. However, if one infects the bladder in a manner that will permit it to persist, say in a rat or rabbit, and then completely transects one ureter and also all of the retroperitoneal tissue on that side (in an effort to block out all of the lymphatics) one still gets an infection in that kidney. The same applies even though blockage has been done prior to infecting the bladder. It would look, then, as though the infection gets to the kidney not via the ureter or via the lymphatics but, rather, by the bloodstream.

In other experiments organisms have been injected into the bloodstream of intact rats or rabbits. Curiously enough, it has been found that only one organism will "take" in the kidney; that organism is Staphylococcus aureus, a coagulase positive organism. Enormous doses of other bacteria can be injected intravenously, but within a few days, they cannot be recovered from the kidney by culture. On the other hand, with Staphylococcus aureus one can continue to culture the organism from the kidney for very long periods of time, and sometimes indefinitely, and severe pyelonephritis supervenes. It looks as if these kidneys are now susceptible to inoculation with other organisms, too, for one can now inject other organisms intravenously and they will "take" in the kidney. We are therefore working on a hypothesis that all pyelonephritis begins, perhaps many years before, as a Staphylococcus aureus infection that may not have even been recognized. But microscopic changes in the kidney have been produced which permit other organisms to take over. Perhaps, this is the reason why one sees patients with chronic pyelonephritis run the whole gamut of organisms, one succeeding another, as periodic culture of the urine is taken from time to time. We do not know whether this is a true hypothesis, but we are working with it in an attempt, at least, to fill a little bit of that vacuum that Dr. Davis has mentioned.

Dr. William H. Boyce (Winston-Salem, N. C.): There are in normal urine approximately 500 mg. of mucosubstances. It has been about 40 years since the Department of Bacteriology at Johns Hopkins introduced a series of studies with regard to the fact that the secretions of normal nasal mucosa are both bacteriolytic and bacteriostatic. We have not investigated these properties of the mucosubstances of the urinary tract, and I think this offers an area for investigation.

We have investigated the protective effect of the larger mucoids of urine for those bacteria which are normally present in urinary infections: E. coli, Aerogenes and Pseudomonas. The large mucoids are particularly protective against drying lyophilization, against freezing at various degrees of hydration, and freezing at minus 18 degrees centigrade. Bacteria which are protected by urinary mucoids derived from normal urine survive these procedures far better than those protected in thioglycolate broth alone.

Finally, there are a host of susceptibles that have been touched on in mice by Dr. DuBois at the Rockefeller Institute. He has demonstrated that colonies of mice (in which the acquired immunity remains essentially the same when subjected to such minor stress as thyroxin or dinitrophenol in doses just enough to slow down their normal rate of growth when challenged with a test dose of bacteria) showed a marked alteration in their resistance to bacterial antitoxins and in their ability to withstand a test dose of pathogenic organisms.

These studies have been extended to the use of 1 per cent sodium citrate (but not sodium lactate), in which it would suggest that under the ordinary stresses and strains of every day living, one's susceptibility to bacterial invasion may markedly alter from day to day, totally independent of one's specific immunologic mechanisms. These studies will eventually lead us to pyelonephritis at the molecular level of one's response to bacterial invasion, immediate and delayed.

Dr. Clyde L. Deming (New Haven, Conn.): I cannot resist saying a word, since Dr. Prather has referred to our professor of medicine, Dr. Paul Beeson, who has been doing a lot of work on catheterized specimens of urine. He has gotten all the services in New Haven scared to pass a catheter. I rise as urologist to defend the urological profession. The urological staff has been catheterizing patients for almost 40 years and has not had any particular difficulty. Our new professor has gotten everyone frightened.

Ex-President Angel of Yale had a great deal of urological trouble, and he left us with this word. He said, "It makes a difference which end

of the catheter you are looking at." He meant by that that one could use a good deal of reason about the use of a catheter.

For the defense of catheterization, I would like to say that we always wash out the bladder with sterile water after catheterization or after passing sounds. Or if your patient empties the bladder, fill the bladder with sterile water and let the patient void following instrumentation. For those patients who have residual urine we wash out their baldders and give them urotropin and acid sodium phosphate. Whenever there is retention of urine, one is more likely to see the infection following catheterization. But the fear of producing an infection in the bladder or kidneys by catheterization need not frighten patients or physicians. More care and thought should be taken in the preparation of the patient and the technique of catheterization.

Dr. John Lattimer (New York, N. Y.): I should like to close by saying that I think the medical men have done us a service by pointing out this vacuum. We have recognized it, as everybody else has, and have established a research laboratory for bacteriological research in the field of genitourinary infections. The mass of information that has been produced has been surprising and gratifying. The implications of some of the things Dr. Zinsser showed you today, I hope, are going to bring about a completely new attack on some of these resistant infections.

We haven't said much about this work so far, but the differences in Krebs' cycle activity of these resistant organisms have been very interesting to us. We have also designed a set of experiments to try to test the remarks of the medical men concerning the perils from catheterization and the prolongation of infection, and hope to have more data for you in the future.

A question has been asked about the high cost of pyridoxine. If you write your patient a prescription and he takes it to the druggist, he will get a bottle of name brand pyridoxine for $20 for 100 pills. If you look into the local drug situation in your town, as we have in New York—we have found that the same drug can be purchased for $3.00 per 100 pills. This is just a word of caution to prevent some of your patients from getting into financial straits as a result of the avoidable mark-up on these drugs.

PRIAPISM; REASONS FOR FAILURE OF THERAPY

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Study of 7 patients with idiopathic priapism reveals 7 features more or less common to all (table 1), which distinguish it from priapism due to neurogenic, vascular, neoplastic or traumatic disorders.

CHARACTERISTICS OF IDIOPATHIC PRIAPISM

1) Previous transient episodes of priapism; prolonged sexual excitement. 2) Erection of corpora cavernosa alone. 3) Presence of dark thick blood, without clots, within corpora. 4) Refilling of corpora with bright blood after early aspiration. 5) Limited subsidence after aspiration. 6) Eventual non-refilling after aspiration. 7) Partial or complete impotency.

It may be revealing to search for causes for priapism and reasons for failure of treatment among these relatively unique attributes.

1) *Previous episodes of priapism; prolonged sexual excitement.* Three of 7 patients previously had experienced abnormally prolonged erections lasting from 3 to 24 hours. This is not a new observation.[1, 2, 3] The fact that recovery from previous episodes occurred spontaneously suggests that in the initial stages, priapism is the overfunction of a basically normal, reversible mechanism. Pertinent is the observation[4] that priapism associated with sickle cell anemia may also spontaneously subside without residual disability. The fact that even priapism secondary to the stasis and thrombosis associated with this disease is reversible again suggests reversible overfunction rather than a gross pathologic derangement.

Four of 7 patients acquired the priapic organ after prolonged intercourse or excessive sexual stimulation. For example, patient M. M. with a tendency toward prolonged erections, had persistent aggressive intercourse with another woman at the time his alienated wife moved in across the street. Patient A. P. had vigorous intercourse because his wife had just returned from the hospital.

An erection, since it is the result of reflex diversion and trapping of blood within the corpora cavernosa, could be self perpetuating if prolonged. Reflex spasm, thickening of the blood by dialysis or change in carbon dioxide tension, or edema or thrombosis near the sites of venous drainage (all of which are implicated by other findings, as we shall see) could act to prolong an initially normal erection.

2) *Corpus spongiosum not involved.* Turgor of the corpus spongiosum and glans was not observed in our patients even when seen early. Thus the whole of the normal mechanism of erection (especially that in the central and peripheral nervous system) is not involved in priapism, but rather only that concerned in the arterial supply and/or venous drainage of the corpora cavernosa. The corpus spongiosum drains directly by way of the venae profundae of the penis, whereas venous drainage from the main cavernous bodies, through the deep dorsal vein, must traverse the prostatic plexus. It has been proposed[5] that thrombosis in this plexus results in the priapism. At least 2 of our patients had marked tenderness and hyperesthesia in the perineum over the site of the prostate, which findings would be in keeping with this concept. However, as noted later, the deep dorsal vein is not found engorged or thrombosed when exposed surgically and so deep thrombosis alone is not the cause.

3) *Priapic penis contains dark blood.* Dark, thick blood has been found invariably when the penis is incised or aspirated.

This shows that vascular stasis is present and hence that venous outflow is less than arterial inflow. Clots were not found, although the blood is thicker than normal. It is probable that some observers attributed the failure of complete

[1] Grond, J.: Priapism. Archivum Chirurg. Neerland, **1:** 283, 1949.

[2] Haar, H.: Zum Priapismus. Med. Klin., **44:** 696, 1949.

[3] Kimbrough, J. C.: Priapism, surgical treatment; case report. Urol. & Cutan. Rev., **54:** 53, 1950.

[4] Campbell, J. H. and Cummins, S. D.: Priapism in sickle cell anemia. J. Urol., **66:** 697, 1951.

[5] Bailey, H.: Persistent priapism. Brit. J. Surg., **35:** 298, 1948.

TABLE 1

	Age	M. M. (40)	E. L. (31)	A. P. (37)	J. S. (40)	R.R. (39)*	C.S. (53)*	B.G. (42)†
1	Previous priapism, or	0	24 hrs. duration	3 yrs. duration	0	"Several times"	0	0
	Onset with prolonged sexual excitement	Prolonged erection & intercourse	0	Prolonged intercourse	Intercourse twice night before	Frequent	Infrequent intercourse	0
2	Flaccid corpus spongiosum	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	Contents dark blood	8 days	16 days	3 days	Not aspirated	11 days	? 6 days	Bled copiously 3 days
4	Refill with bright blood	8 days	16 days	3 days	Not aspirated	11 days	Pressure dressing	3 days
5	Percentage of temporary subsidence with aspiration	20%	40%	30%	Massage at 20 days 30%	40%	60%	0%
6	No refilling after aspiration	Varying	23 days	6 days	20 days	Varying	Pressure dressing	9 days
7	Potency	Partially potent	Slight basal erection	Intercourse with slight basal erection	Impotent	1½ inches of base erectile	Impotent	1 inch of base erectile

* Data with permission of Dr. Willard E. Goodwin.
† Data with permission of Dr. Frederick S. Howard.

subsidence after aspiration to inaccessible blood clots, whereas as we shall see, subsidence is incomplete because of edema of the myriad trabeculae in the corpora.

It has been demonstrated[6, 7, 8] that during vascular stasis, the carbon dioxide content of the blood rises, which in turn increases blood viscosity. This "thickening" may also be a factor in prolonging the erection, since thick blood can escape less easily through restricted venous channels. Menzel[9] has described just such increased viscosity resulting in priapism in a 5-year-old boy. Comparable is the priapism associated with sickle cell anemia[10] in which capillary stasis and obstruction prolong the erection. The venous congestion resulting from normal erection of the penis leads to decreased oxygen tension, and so to increased sickling of the red blood cells. This in turn causes more stasis, probably with consequent thrombosis and venous occlusion.

The obstruction to outflow from the corpora lies near the cavernous bodies themselves since exposure of the deep dorsal vein[11, 12, 13] proves it to be empty. Conti[11] described "polsters" where the collateral veins empty into the deep dorsal vein. These, as part of the mechanism of normal erection operating to cause stasis of blood, may be the site of an irreversible venous obstruction which then results in priapism. Also playing a part, as suggested by Kiss,[14] is impedence of venous outflow by compression of the veins against the fibrous coats of Buck's fascia. It is probable that venous outflow is the same whether the organ is erect or flaccid,[11] and that only enough blood circulates to provide nourishment for the tissues.

That some of the channels for venous outflow may again become patent is shown by 2 reported cases. In one, vigorous massage and compression on the twentieth day expressed enough blood to reduce the organ by one-third.[15] In another case,[13] a ganglionic blocking agent was given on the ninth day. During the resulting hypotension, aspiration achieved partial subsidence, with only slight returgescence after stopping administration of the drug. Whether this effect was attained by the reduction in the ingress of blood by the low blood pressure, by the peripheral action of the ganglionic blocking agent on the arteriovenous connections in the penis, or by timely aspiration has not been made clear. In some of our cases of even shorter duration, refilling did not occur after aspiration.

4) *Refilling with bright blood.* The corpora cavernosa immediately refilled with arterial blood in six of the patients the first time the intracorporeal pressure was reduced by aspiration or incision. (In the seventh case, aspiration was not done.) In one case this refilling resulted in serious hemorrhage at the site of incision (B. G.). The shortest interval after the onset of priapism that this was observed was 3 days, but in two cases, the corpora refilled after intervals as long as 11 and 16 days.

These observations show that in the early stages of priapism, the arterial supply to the erect organ is still patent and that the mechanism of erection is still in action (arterial inflow with reduced venous outflow). Pressure dressings after aspiration are usually not effective because they must be tight enough to prevent inflow at arterial pressure, hence they cause gangrene.

Later in the course of the disease (cf. cases M. M. and R. R.) aspiration is followed by the slow rise and fall of the erection; the penis never becomes completely flaccid, but neither does it reach full erection. This transitional stage is interesting because it shows that the stimulus to erection is still active, and seems to remain so until later occlusion of the arterial supply occurs.

5) *Limited subsidence on aspiration.* The recorded estimates of the degree of return toward flaccidity in the 7 cases are subject to the prejudices of the observer, but varied from 20 per cent to 40 per cent decrease in size excepting one instance in which a 60 per cent reduction occurred. Such partial subsidence is uniformly re-

[6] Rotenberg, M. J.: Du role de la viscosité du sang dans la pathogénie du priapisme. J. d'urol., **39:** 508, 1935.

[7] Chauvin, E.: Quelques considérations sur la pathogénie du priapisme; à propos de deux cas personnels. J. d'urol., **46:** 224, 1938.

[8] Cuccioli, U.: Contributo allo studio del priapismo cosidetto idiopatico. Arch. ital. urol., **21:** 52, 1944.

[9] Menzel, Von Dr. E.: Der Priapismus beim Kinde. Zbl. Chir., **78:** 89, 1953.

[10] Diggs, L. W. and Ching, R. E.: Pathology of sickle cell anemia. South. Med. J., **27:** 839, 1934.

[11] Conti, Giuseppe: L'érection du pénis humain et ses bases morphologicovasculaires. Acta Anatomica, **14:** 217, 1952.

[12] Herzog, W.: Zur pathogenese des Priapismus. Arch. klin. Chir., **277:** 422, 1953.

[13] Ulm, A. H.: Treatment of primary priapism with arfonad. J. Urol., **81:** 291, 1959.

[14] Kiss, F.: Anatomisch-histologische Untersuchungen über die erection. Ztschr. f. d. ges. Anat., **61:** 455, 1921.

[15] Brody, H. S., Lahr, P. A. and Carroll, W. A.: Primary priapism: A new treatment. J. Urol., **78:** 153, 1957.

ported by previous observers as well. We may well ask, should not complete flaccidity follow thorough irrigation and evacuation of the cavernous bodies?

One reason might be that fresh blood refills the corpora. But in 3 cases, a second aspiration was not followed by refilling and yet subsidence was only partial. Clots might remain behind but these have not been demonstrated. Our biopsy studies have shown the real reason. The delicate septa which occupy the cavernous spaces when the normal organ is flaccid (fig. 1) become edematous and thickened after days of erection, thus virtually filling the free space in the organ (fig. 2, *A*). This explains too the increase in size and turgidity of the priapic penis when compared with one in normal erection.

6) *Eventual non-filling after aspiration.* If aspiration is done late enough in the course of the disorder (in this series at least after the sixth day), it is not necessarily followed by refilling of the cavernous bodies. For example, in one case, aspiration on the third day was accompanied by returgescence, but re-aspiration on the sixth day resulted in 30 per cent subsidence of the erection. This improvement persisted.

It is apparent, then, that after a time, changes occur within the organ which differ from those in the normal erection. Arteriolar closure by clotting edema, or fibrosis, or a combination of these, appears to be operative.

Herzog[12] injected the dorsal artery of the penis on the twenty-second day and got no filling of the corpora cavernosa. This finding agrees with the observation that the corpora do not refill after late aspiration, and that they do not bleed when incised later in the course of the disease.

7) *Impotency.* That truly normal erections are ever regained after prolonged priapism is doubtful. A good reason for this, as we have shown, is that the inflow of blood to the cavernous spaces is eventually obstructed, perhaps irreversibly. However, in four of the cases reported here, erection of the base of the penis persisted sufficiently to allow intromission. Such proximal erections are instructive. They show that the part of the intracorporeal mechanism farthest from the arterial source can be irreversibly damaged while that nearest the blood supply retains its erectile activity.

A second reason for impotency, we have discovered, is that the edematous changes in the septa during the active phase of the disorder (fig. 2, *A*) progress to fibrosis (fig. 2, *B*). Not only is there little or no room for blood in these spaces, but probably more important, there is serious disruption of the arteriovenous connections. Hence filling cannot occur.

NORMAL ERECTION OF THE PENIS

Vascular aspects. Erection is achieved by increasing the quantity and the pressure of blood in the cavernous spaces confined by Buck's fascia. This increase theoretically may be the result of heightened resistance to the drainage of blood from the corpora, or of greater arterial inflow (fig. 3). The end result is a 4 to 5 fold increase in

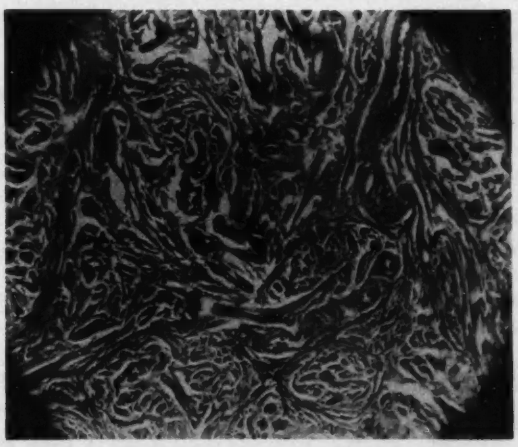

FIG. 1. Photomicrograph of septa in corpus cavernosum from normal penis. Note delicacy of fronds. (× 100)

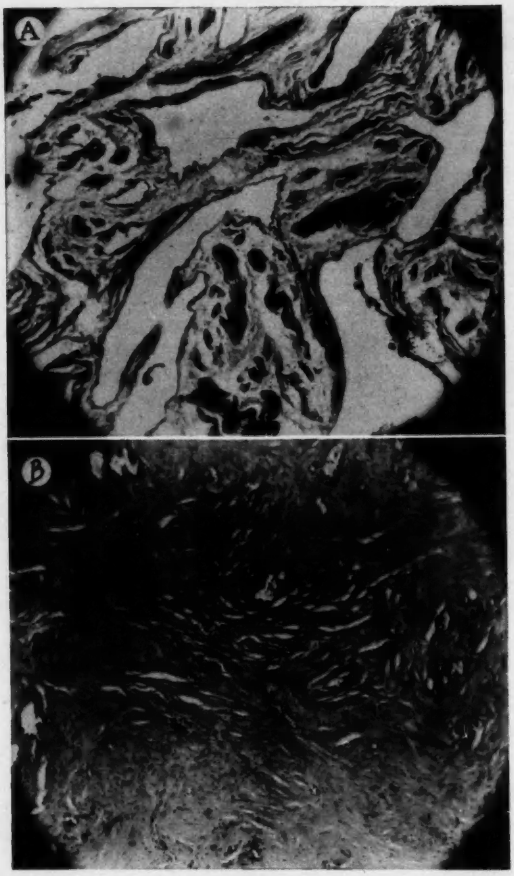

FIG. 2. *A*, septa after 6 days of priapism. Note marked edema of septa accounting for limited subsidence of erection after aspiration. (× 100). *B*, septa from penis 2 years after priapism. Note consolidation and fibrosis, which virtually eliminates blood from entering lacunae and which provides reason for impotency. (× 100).

penile volume and a final pressure closely approaching that of the carotid artery.[16]

As long ago as 1668, de Graaf obtained erection in the cadaver by injecting water through the dorsal artery of the penis. He thought that contraction of the perineal muscles produced venous stasis, but Cadiat in 1877 was able to demonstrate that the vessels passed through protective canals, such that contraction of the perineal musculature could exert no effect on the veins. Blockage of the funnel vein of Kiss, which had been described as containing valves, was thought to be the initiating factor by Grond,[1] but in dogs, Henderson and Roepke[16] showed that erection was not impeded by removal of the ischio- and bulbocavernosus muscles. This was later confirmed in cats by Semans and Langworthy.[17] Contraction of these muscles can increase the erection momentarily by forcing blood distally from the bases of the corpora.

On the other hand, support for the "arterial" theory came from Ebner's concept that the longitudinal elevations of the arterial intima (polsters) (fig. 4, *A*) previously described by

[16] Henderson, V. E. and Roepke, M. H.: On mechanism of erection. Am. J. Physiol., **106:** 441, 1933.

[17] Semans, J. H. and Langworthy, O. R.: Observations on the neurophysiology of sexual function in the male cat. J. Urol., **40:** 236, 1948.

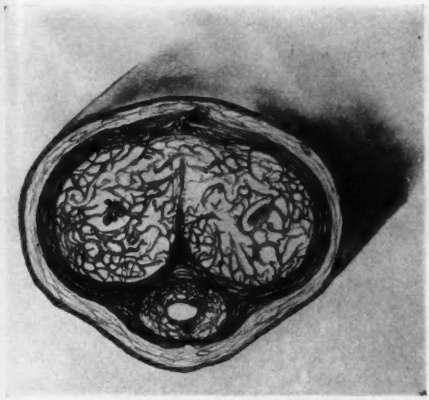

FIG. 3. Schema of cross section of erect penis showing central arteries and arterioles, and deep dorsal vein with tributory venules. Obstruction to venous return may occur at juncture of cavernous spaces with venules.

Ercolani in 1869, contracted to act as valves to decrease the inflow of blood and keep the organ flaccid. Subsequent workers have supported this concept with further histologic evidence.[18]

A middle course between these opposing theories has been opened recently by Conti[11] working at the University of Padua, a center for the study of arteriovenous anastomoses. Figure 4, *B* shows the circulation of blood in the flaccid penis. The polsters in the artery distal to the A-V anastomosis decrease the arterial caliber and shunt the blood away from the corpora. The polsters in the drainage veins, on the contrary, are relaxed so that drainage is complete.

In erection (fig. 4, *C*), the cushions in the shunt as well as those in the drainage veins are closed, whereas the arteries are wide open. The cavernous sinuses become engorged and erection results.

A considerable body of evidence is now available to show that vasodilation is primarily responsible for erection. The lumbar sympathetics act by inhibition of vasoconstriction.[19] More important is the vasodilation of the arterioles by way of parasympathetic nerves from S2-4, which have been demonstrated by direct stimulation in dogs.[16] Since there had been no real evidence for active occlusion of the venous outflow, it was concluded that erection resulted from too much blood for the fixed-caliber veins to carry off. This concept is agreed upon by subsequent workers, and is not vitiated by Conti's findings, which are rather an extension of it.

That arterial inflow is the primary factor is borne out by the experimental occlusion of the aorta in cats during erection by Semans and Langworthy.[17] Erection subsided 2 minutes after occlusion, and could not be restored by stimulation of the sacral nerve root. Similar observations have been made in patients with arterial occlusion equal to obstruction of both hypogastrics or of one iliac artery and part of the other. These patients are unable to have erections, and those with somewhat lesser occlusions can obtain an erection but lose it immediately on intromission.

Neurologic aspects. Erection is initiated either by penile stimulation via the pudendal nerve to the lumbar and sacral centers or by psychic stimuli through the diencephalon and down the cord to the same spinal area (table 2). From the lumbar center, sympathetic stimuli from L2-4 pass to the vessels of the penis and inhibit vasoconstriction.

Much more important is the effect of parasympathetic stimuli passing through S2-4 via the "nervi erigentes" carried in the pelvic nerves. These have a direct vasodilating effect,[16] and cause filling of the cavernous spaces at a rate greatly in excess of the rate of venous outflow (table 2).

That erection in the human is dependent on this nerve supply is shown by Munro's[20] analysis of 84 paraplegics, 74 per cent of whom were capable of having erections. He found that erections were prevented only if the sacral segment of the cord was destroyed, or if the cauda equina and parasympathic pelvic plexus was lost (patients with an autonomous neurogenic bladder and absent bulbocavernosus reflex).

Subsidence of erection occurs by vasoconstriction on stimulation of the sympathetic nerve supply, the same stimulation that causes the preceding emission of semen from the seminal vesicles, ejaculatory ducts and prostate gland (smooth muscle).

[18] Stieve, H.: Harn- und Geschlechtsapparat. in v. Möllendorff, W. Handbuch der microskopischen Anatomie des Menschen. vol. 7/2, p. 327, Berlin: Julius Springer, 1930.

[19] Whitelow, G. P. and Smithwick, R. H.: Some secondary effects of sympathectomy. With particular reference to disturbance of sexual function. N. Eng. J. Med., **245:** 121, 1951.

[20] Munro, D., Horne, H. W. Jr. and Paull, D. P.: The effect of injury to the spinal cord and cauda equina on the sexual potency of men. N. Eng. J. Med., **239:** 903, 1948.

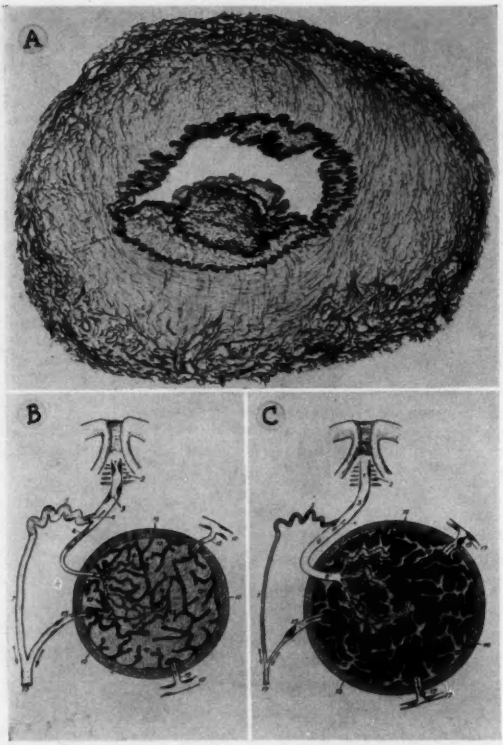

FIG. 4. *A*, "polster" in artery to glans. From Stieve,[18] p. 327. *B*, circulation in flaccid penis. Blood from artery to corpora cavernosa (1) is directed into superficial arteriovenous connection (5) by obstructive arterial polsters (6). Helical arteries (8) are obliterated similarly. (From Conti,[11] p. 259). *C*, circulation in erect penis. Now polsters in arteriovenous connections (5) are active, and blood is directed through helical arteries (8) into cavernous spaces (10). Venous stasis results from obliteration of efferent veins (15). (From Conti,[11] p. 260).

ABNORMAL ERECTION

Priapism might be defined as persistent penile erection without sexual excitation.

A classification, modified from Hinman, Sr.[21], can be made as follows:

A. Neurogenic
   1. Psychic stimuli
   2. Direct nerve stimulation (in cord, pudendal nerve, or nervi erigentes)
   3. Reflex from local stimuli

B. Mechanical
   1. Thrombosis or pseudothrombosis (increased blood viscosity)
   2. Hemorrhage and hematoma
   3. New growths in penis
   4. Local inflammation

C. Cause not assigned (idiopathic priapism).

Knowing something of the mechanism of erection, we can postulate areas where dysfunction could produce priapism (table 2).

On the *neurologic level*, psychic stimuli might prolong erection unduly, but since the pain of prolonged erection eliminates erotic sensations, this is most unlikely.

Central nervous system disease, however, produces priapism. Typical of the neurogenic group are those cases of priapism associated with high spinal cord injuries. In Munro's series[20] of 221 patients with cord lesions at all levels, 10 per cent had priapism. It was most common in the group with cervical injuries (14 per cent), but occurred in the thoracic (6.5 per cent), lumbo-

[21] Hinman, F.: Priapism. Report of cases and a clinical study of the literature with reference to its pathogenesis and surgical treatment. Ann. Surg., **60**: 689, 1914.

TABLE 2

NEUROGENIC: psychic stimuli ↘ / local sensation ↙	1. Previous episodes; prolonged sexual excitement
lumbar-sacral centers	
↓	
arteriolar vasodilation in corpora	
↓	
ERECTION	
↓	
stasis	2. C. cavernosa only
↓	3. Dark thick blood
increased CO_2 tension	4. Refilling after aspiration
↓	
MECHANICAL: increased blood viscosity; edema	5. Limited subsidence
↓	
greater insufficiency of venous drainage	
↓	
PRIAPISM	
↓	
arteriolar occlusion; fibrosis	6. Eventual non-refilling
↓	
SUBSIDENCE	7. Impotency

sacral (5 per cent) and partial cauda equinal (3 per cent) groups as well.

Increased sensation from the posterior urethra, through reflex activity, could prolong erections—and treatment has often been aimed at reduction of local sensation. But little evidence can be found in the reported cases or in our own experience for posterior urethral disease either from the patients' histories or from the findings on examination. At most, such urethritis is a contributory factor.

At the local level, *mechanical factors* are responsible. These probably do not operate by prolonging or increasing the vasodilation and inflow of blood, but rather by increasing the existing insufficiency of the venous outflow (table 2).

For example, as noted in cases of priapism with sickle cell anemia, venous congestion leads to decreased oxygen tension, which increases sickling of the red blood cells which in turn produces more stasis, finally resulting in thrombosis and occlusion with consequent priapism.

Similar examples of the effects of local mechanical disorders are priapism secondary to infiltration of the corpora by carcinoma or leukemia. Trauma at the base of the penis also can cause priapism by disrupting the pathways for venous drainage.

In addition to the groups due to neurogenic and the local cause is the most interesting group, *idiopathic priapism*, in which no disease can be implicated.

A *working hypothesis* which accounts for most of the observed facts in this idiopathic group is as follows:

1) Erection is prolonged by psychic or local excitatory factors, resulting in

2) venous stasis;

3) the viscosity of the blood rises from the increased carbon dioxide tension, producing

4) relative venous occlusion at the site of juncture of the cavernous spaces with the collecting veins;

5) edema of the trabeculae fills the corpora and further reduces the chance for venous outflow;

6) eventually, occlusion of the arterioles occurs, allowing aspiration to reverse the processes; and finally,

7) fibrosis in the trabeculae combined with disruption of the arteriovenous supply mechanism makes adequate erections impossible.

TREATMENT

That reversal of priapism is difficult is suggested by the following partial list of recorded therapeutic measures.

Nerve and muscle control: spinal and caudal anesthesia, anectin, pudendal block, lumbar sympathetic block, intravenous procaine, general anesthesia.

Removal of blood: aspiration, irrigation, incision, tube drainage.

Removal of "clots": heparin, dicumarol, varidase, massage.

Prevention of return filling: pressure dressing, ganglionic blockade via hypotension, ligation of dorsal artery.

Reopening of venous drainage: ganglionic blockade, anticoagulants, division of ischiocavernosus muscle.

Anti-androgenic therapy: stilbestrol.

Urethral effect: bladder sedative, etc.

Sedatives: demerol, meprobamate, nembutal, etc.

None of these measures have been really effective. "New" methods are often reported, but critical examination of results leaves the student unsatisfied.

The basic reasons for failure of the various treatments are: 1) they do not restore venous drainage; and 2) they do not eliminate the progressive damage to the local erectile mechanism.

Methods of treatment so far devised have not effected increased venous drainage. The possible exception is the use of ganglionic blockade,[13] but further experience will be needed, since in the one case reported, aspiration was done simultaneously and treatment was instituted rather late in the course of the disorder (ninth day). To be effective, measures aimed at increasing venous drainage must be applied early, even though this is the time that the arterial supply is unimpeded and immediate re-erection might be expected.

The second reason for failure of treatment is a corollary of the first. If an early balance cannot be achieved between arterial filling and venous drainage, the septa in the corpora swell from edema, eventually becoming irreversibly fibrosed. Of greater importance is the occlusion of the arteriovenous mechanisms (demonstrated by the absence of refilling after aspiration or incision later in the course). This allows the immediate "cure" so many have reported, since the erection is reduced, but it prohibits a real cure because good erections can probably never occur again. The ability for erection of the base of the penis (nearer the arterial supply) not infrequently persists but verifiable reports of completely normal erection following treatment for idiopathic priapism are difficult to find.

Since no effective or specific treatment has been demonstrated, it would seem best: 1) to be certain that neurologic, systemic or local mechanical factors are not operative; 2) to provide sedation, analgesia and local hypothermia, and 3) to simply aspirate the corpora aseptically after 6 or more days, repeating the aspiration at 3 day intervals if re-erection occurs. A trial of a ganglionic blocking agent[13] would further our knowledge of this particular treatment. In any case, it would be advisable not to promise the patient a perfect result.

SUMMARY AND CONCLUSIONS

Seven cases of idiopathic priapism are analysed for factors in common (previous episodes, sparing of corpus spongiosum, presence of dark blood, limited subsidence from aspiration with frequent returgescence, eventual non-refilling, and final impotency).

A probable causal sequence is: a prolonged erection from psychic or local stimuli is accompanied by venous stasis, which increases the viscosity of the blood, producing relative local venous occlusion. This results in edema of the trabeculae and closure of the arteriolar blood supply, and very gradual subsidence of erection. Fibrosis prevents subsequent erections.

Treatment is generally not effective. Impotency is the usual end result.

DISCUSSION

DR. WILLIAM W. SCOTT (Baltimore, Md.): The cause of priapism is not always as Dr. Hinman describes. A case which we saw recently will be reported by Dr. Horst Schirmer and Dr. Fred Burt of our resident staff.* This patient was seen early in the course of his priapism and was not benefited by heavy sedation or a spinal anesthetic. In order to gain knowledge regarding the mechanism of production of his priapism, an exploratory operation was performed. The dorsal vein was first aspirated, and contrary to what one might have expected, the blood in the dorsal vein was bright red, not dark. On opening one of the corpora through a small incision, rather than dark blood, bright red blood was encountered.

On the basis of these findings and after discussion at our Tuesday morning rounds, a decision was made to tie off one pudendal artery, this case of priapism being asymmetric. The pudendal artery was exposed without injury to the nerve, and application of a bulldog clamp to the artery resulted in an immediate flaccidity of the penis. Therefore, the pudendal artery was doubly ligated and divided. The erection promptly went away. It has not recurred, this being some six months ago. This man is potent.

DR. WYLAND F. LEADBETTER (Boston, Mass.): I am interested in Dr. Hinman's and Dr. Scott's comments because this last year we had a case of priapism for which various attempts were made to aspirate the corpora, to give spinal anesthesia, and use other medication without success. Finally, in desperation, I suggested that the resident tie both pudendal arteries with fine plain catgut. He did this with prompt improvement in the priapism. It seemed to me afterwards that we probably waited and tried various other procedures too long because the damage which Dr. Hinman points out had already occurred in this case.

I believe that the only logical way of treating priapism is to ligate the branches of the pudendal arteries in the perineum and then aspirate the corpora. This would seem to me to prevent the further engorgement of the cavernous spaces in the penis and allow nature to bring things back to normal.

In regard to Dr. Nesbit's report of thromboangiitis obliterans of the spermatic vessels, I might suggest that there are several causes for granulomatous lesions involving the spermatic cord. For instance, recently we saw a young man from Cuba who had a small mass in his scrotum. In the course of studying his case, an x-ray of his chest showed multiple areas of infiltration and he was found to have a strongly positive reaction for histoplasmosis. We removed this lesion which involved the vessels of the spermatic cord and found a granuloma which was entirely compatible with the diagnosis of histoplasmosis. This illustrates the fact that a general evaluation in these patients with obscure situations is desirable.

DR. REED NESBIT (Ann Arbor, Mich.): If the Chair will permit, I would like to use the time to end my discussion on another subject entirely. I will get through within three minutes.

My associate, Dr. Jack Lapides, suggested only recently that interstitial cystitis might be due to some vascular disturbance. He gave a patient a vascular dilating agent, priscaline. This woman had normal frequency of urination and comfort thereafter until he deliberately gave her placebos, and under the placebos she had an immediate return of all of her symptoms.

There have been three other patients treated by this same method, two of them my own private patients, in whom the lesions were rather small, but the symptoms excessive, and in whom the appearance of the bladder was one where the observer is aware of a tremendous amount of vascularity. These patients, only recently put on priscaline, have been completely comfortable and have had normal frequency. One patient—the lady whom you sent to us, Dr. Ormond—with that tremendous big lesion, was not improved by this form of medication. The observations on these few patients suggest that vasodilating agents may provide significant benefits in some patients who suffer from interstitial cystitis. Time will tell, and perhaps each of you can give the method a trial and let us know whether good or bad results occur.

DR. LEADBETTER: What is the dosage?

DR. NESBIT: 25 mg. q.i.d.

DR. FRANK HINMAN, JR. (San Francisco, Cal.): I think that Dr. Scott's patient fits into a somewhat different group from the one I was talking about. I would like to know first what the effect of bilateral pudendal artery on erection would be. His would seem like a very direct attack on this case of priapism but not on the over-all problem. It would only be suitable for a peculiarly unilateral patient, which is not typical.

* Urol., **83:** 60–61, 1960.

THROMBOANGIITIS OBLITERANS OF THE SPERMATIC CORD

REED M. NESBIT AND NORMAN B. HODGSON

From the Department of Surgery, Section of Urology, University Hospital, Ann Arbor, Mich.

Leo Buerger in 1908 separated thromboangiitis obliterans from the undifferentiated pool of peripheral vascular diseases and established an entity that bears his name. The process has since been found in all parts of the body. It is a granulomatous panarteritis and panphlebitis. No cause has as yet been determined, but the deleterious effects of smoking are well documented.

Quite rarely the disease has been found to involve the vessels of the spermatic cord. Buerger described one such case which clinically he had difficulty differentiating from tuberculosis. Indeed this differentiation has been a primary problem in most of the cases reported.

Six other cases have been reported: those of McGregor and Simson in 1929, Tartakoff and Hazard in 1938, Mathé in 1940, Maryhofer in 1947, Mathis and Claret in 1951 and Russell Howard in 1950.

All of the cases described to date have occurred on the left side, and other clinical differential diagnoses besides tuberculosis of the spermatic cord were thrombosis of the pampiniform plexus and lymphoblastoma.

Two cases have been seen on the urology service of the University of Michigan Hospital and comprise the basis of the present report. Both of these have occurred in the left spermatic cord. For one the primary impression preoperatively was thrombosis of the pampiniform plexus, while for the second, although Buerger's disease was considered, the primary preoperative diagnosis was tuberculosis of the spermatic cord. The first case was seen and treated in 1947 and the second in 1956.

CASE REPORTS

Case 1. J. W., U.H. No. 625512, a 26-year-old male student, was first seen at the University Hospital on October 21, 1947 with a 5 week history of swelling of the left testicle. This was associated with a dull aching pain in the scrotum which radiated into the left inguinal region. He gave a past history of a left varicocele since 1941. Examination showed an exquisitely tender mass in the left scrotum just superior to the testis. The rest of the physical examination and all of the laboratory studies were normal. Chest film was normal as was the O.T. skin test.

Conservative management was used and on re-examination 1 week later the process appeared as an indurated mass with a pea sized tender nodule just superior to the testis. It was followed and shortly gave the impression that there was extension of the process into the inguinal canal. With the working diagnosis of thrombosis of the pampiniform plexus exploration was carried out November 12.

At operation the surgeon felt there might be a neoplasm of the epididymis with extension along the spermatic cord so an orchiectomy along with resection of the thickened structures of the spermatic cord was performed.

Gross pathologic description showed an enlarged and thickened epididymis and vas deferens. The testis appeared to be normal.

Microscopic analysis showed "a granulomatous phlebitis with thrombosis and organization. The individual granulomatous foci suggest tubercles." The pathologist (C. V. W.) goes on to state, "However, for a number of years such processes have been interpreted as nontuberculous and usually, as an early or acute phase of Buerger's disease. There were no foci in the vas."

The postoperative course was uneventful. Complete evaluation for evidence of Buerger's disease elsewhere in the body failed to demonstrate abnormality other than that the digits were cooler than the rest of the body. There was also severe hyperhydrosis of the hands and feet.

In October 1956, nine years following operation, the patient was re-evaluated by his private physician who found no evidence of Buerger's disease either locally or elsewhere.

Case 2. G. B. U.H. No 846865, a 24-year-old carpenter of Roumanian extraction, was admitted July 22, 1956 with a 2 week history of a hard, tender lump in the left scrotum. There had been no change in size since it was first discovered. He had no other genitourinary symptoms. The only other abnormal findings in the history were

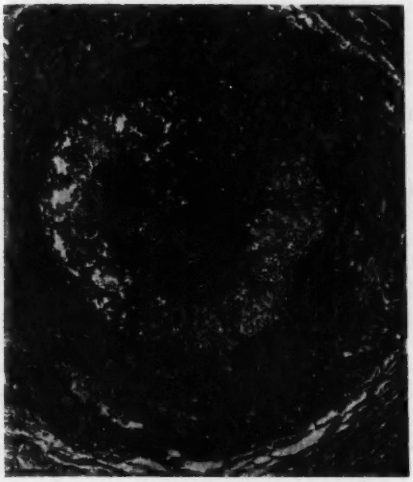

FIG. 1. Case 1. Low power section shows thromboangiitis obliterans in vessel adjacent to epididymis. Note foreign body giant cell.

FIG. 2. Case 2. High power section of acute thromboangiitis obliterans in artery adjacent to vas deferens.

bilateral perforations of the ear drums from otitis media as a child, typhoid fever at age 11, and maternal death from pulmonary tuberculosis when she was 29. There was no history of venereal disease.

Examination showed thickening of the left vas deferens extending from just below the external inguinal ring to a point just within the epididymis. The scrotal contents were normal, as was the rest of the physical examination.

Laboratory studies were normal. Chest films showed a healed primary tuberculous lesion in the lung, and the O.T. skin test was positive.

At operation an apparent inflammatory process was found involving the vas deferens and the tip of the globus minoris of the epididymis. The involved tissues were resected. The postoperative course was uneventful. Three 24 hour urine specimens taken for acid fast bacilli were negative on culture and guinea pig inoculation.

The pathologic report stated that in the vicinity of the epididymis some of the veins show organizing thrombi. In the thrombotic material there is a granulomatous component with giant cells. It was felt to represent an acute stage of thromboangiitis obliterans.

At the first postoperative visit one month later there was suggestion of recurrence of the process in the adjacent tissues and some extension of the process up the spermatic cord. On a subsequent visit 3 months later there was no evidence of inflammation or induration or abnormality other than a soft, well healed scar. Complete evaluation for other evidence of Buerger's disease was negative.

From existing medical knowledge it is impossible to state categorically that Buerger's disease is a discrete pathologic entity. The diagnosis is made histologically, but perhaps in actuality the picture represents a number of vascular lesions.

This report is not meant to be a discussion of the broad field of peripheral vascular diseases. At the time of operation in each case the vas deferens and surrounding fascia appeared grossly to be abnormal, yet the microscopic sections revealed no abnormality whatever in the vas deferens or the epididymis, the sole abnormality being in the blood vessels. If Buerger's disease is a discrete entity, the findings in the two cases suggest that it can be a localized process in the spermatic cord. Limited surgical excision of the inflamed vessels has apparently been as successful in eliminating the process and the ischemic pain as the more radical treatment of orchiectomy and resection of the scrotal spermatic cord.

CONCLUSION

Two cases of Buerger's disease of the spermatic cord have been reported. Both were treated

surgically under the working diagnosis in one case of thrombosis of the pampiniform plexus or neoplasm of the epididymis, and in the other of tuberculosis of the spermatic cord. Nine year followup in one case fails to reveal any evidence of persistence or recurrence of the disease locally of systemically, and a 5 month followup in the other case is likewise normal.

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HEMINEPHRO-URETERECTOMY: COMPARISON OF ONE-STAGE AND TWO-STAGE OPERATIONS

ORMOND S. CULP

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Heminephrectomy has been accepted as o of the most valuable procedures in the repertoire of the urologic surgeon. To avoid confusion the term should be used only to indicate excision of one segment of a kidney with duplication of the renal pelvis. The operation has been employed universally as the practical solution to a great variety of clinical problems. Opinions have differed, however, regarding the calculated risks of heminephrectomy, the technique of choice and the best treatment of the corresponding ureter.

To help clarify some of these controversial facets, 100 heminephrectomies performed at the Mayo Clinic from 1936 through 1957 were reviewed. Ages of the patients varied from 4 months to 66 years (table 1), with 35 per cent in the first decade. Six patients were less than 1 year of age. The ratio of females to males was 3:1. At least some of this difference can be attributed to the higher incidence of detectable ectopic ureteral orifices in female patients.

Indications for operation included benign cyst (2 cases), calculi (14 cases), infected hydronephrosis (51 cases), and urinary incontinence (33 cases).

In 10 cases the entire ureter draining the affected segment was removed at the time of heminephrectomy. Only that portion of ureter which was readily accessible through the lumbar incision was excised during the other 90 primary operations.

TECHNIQUE

The literature abounds in proposed variations in surgical techniques. Success invariably depends upon the ability of the surgeon to 1) choose the proper amount of tissue to excise, 2) control bleeding during the procedure and 3) prevent postoperative hemorrhage and other serious complications. As long as all three prerequisites are fulfilled, it seems to matter little how they have been achieved. Most so-called refinements in technique are merely embellishments.

Most of the diseased segments in this series were identified by telltale scarring, atrophy, or the distinctive cleft. In a few instances when the line of demarcation was indiscernible or followed an oblique angle that threatened to compromise the cortex to be saved, the abnormal pelvis was opened to be certain of its ramifications. This did not result in complications and undoubtedly it conserved renal tissue.

When a separate blood supply to the diseased segment could not be demonstrated, a rubber-shod clamp was applied to the pedicle in most instances.

A transverse wedge-type resection (fig. 1*a*) was employed most frequently. Any communication with the remaining pelvis usually was sutured and spurting vessels were transfixed. The cortical defect invariably was closed with mattress sutures of chromic catgut tied snugly but not tightly over pads of fat, supplemented by a continuous suture in the capsule (fig. 1*b* and *c*). If there was insufficient capsule or if the outer part of the cortex could not be approximated, a pad of fat was tied into the raw area (fig. 1*c'*). Allegations that this type of closure will produce too much necrosis are discounted by the normal postoperative appearance of most of the remaining segments and by the fact that none of these patients has developed postoperative hypertension.

When primary complete heminephro-ureterectomy was performed, a second lower abdominal incision was used for removal of the pelvic portion of the ureter.

COMPLICATIONS

There were no surgical deaths in this series. Nonfatal complications attributable to this particular type of procedure occurred in 9 cases.

Urinary fistula. One fistula of ureteral origin that followed complete heminephro-ureterectomy failed to heal and the remaining segment of the kidney had to be removed.

Chronic sinus. Four patients continued to have purulent drainage (free of urine) for 5 to 22 months. One sinus eventually healed spontaneously, another closed after curettage, and two were excised successfully.

Hydronephrosis. In 2 cases total heminephro-

TABLE 1. *One hundred heminephrectomies*

Age, years	Sex		Total
	Male	Female	
⅓–9	4	31	35
10–19	1	11	12
20–29	3	16	19
30–39	4	8	12
40–49	5	9	14
50–59	3	1	4
60–66	4	0	4
Total	24	76	100

ureterectomy resulted in stricture of the remaining ureter and secondary hydronephrosis. Ureteral dilatation did not suffice, so the remainder of the kidney was removed in both instances.

Functionless remainder. Two patients who had only partial ureterectomy during the initial procedure were left with functionless remaining segments. One of these was removed and showed pyelonephritic atrophy. The other awaits operation.

Others. Four additional patients had postoperative misfortunes that may occur even when there has been no surgical procedure. There was 1 case each of pneumonitis, pulmonary infarction, staphylococcal enteritis (due to use of a broad-spectrum antibiotic) and unexpected hemorrhage from a duodenal ulcer. None of these complications occurred during secondary operations. All 4 patients recovered.

It is apparent, therefore, that the greatest danger inherent in operations of this type is compromising the blood supply to the remaining ureter or the other segment of the kidney. It is noteworthy that three of the five vascular disasters in these 100 cases followed complete heminephro-ureterectomy. It seems prudent to consider the situations in which total and partial ureterectomy were employed and their justifications.

CLINICAL APPLICATIONS

Cortical cyst. Each of the benign cysts was so large that it had destroyed most of that segment of the kidney. Consequently, heminephrectomy assured a better result than trimming off the wall of the sac. Only the adjacent ureter was removed in both cases.

Calculous disease. Partial ureterectomy was employed in the 14 stone-bearing patients. Complete duplication of the ureter was demonstrated in only 5 cases. Each of these supernumerary orifices was intravesical.

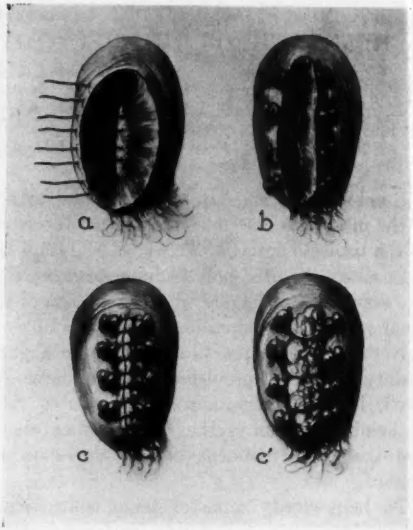

FIG. 1. Closure of cortical incision. *a*, Mattress sutures of chromic catgut placed through the cortex, *b*, tied over pads of fat and, *c*, reinforced with continuous catgut suture in the capsule. *c'*. Fat tied into exposed portion of cortex which is devoid of capsule.

Most of the problems in this group were relatively simple, but in a few situations more advanced calculous disease was seriously complicated. For example, one patient with bilateral duplication had calculi in both lower segments (fig. 2*a*). The lower right segment was removed with a gratifying result (fig. 2*b*). The asymptomatic left kidney was merely observed until the patient became acutely ill 6 years later with a perinephric abscess (fig. 2*c*). The abscess was still draining profusely 6 months after it had been incised. Heminephrectomy was performed under most disagreeable circumstances. Although the flank is now healed, the remaining upper left segment is functionless. The patient feels well and his blood urea measures only 52 mg. per 100 cc, but in all probability more timely surgical intervention might have simulated the result on the right.

If a patient already is living on salvaged cortical tissue, one should not procrastinate about protecting diminished renal reserve. The risk

of perinephric abscess in advanced calculous disease should not be ignored.

Fortunately none of the ureteral stumps in this group contained calculi and none has caused further trouble.

Eighty patients with infected hydronephrosis or incontinence had complete duplication of the ureter. They conformed to three distinct categories: 1) no ureteral ectopia or incontinence, 2) ureteral ectopia without incontinence and 3) ureteral ectopia with incontinence.

Without ureteral ectopia. In 24 cases the extra ureteral orifice was found inside the bladder. Five orifices were associated with ureteroceles and two were located within diverticula. In three instances the ureter to the upper segment ended blindly in the lumbar region (fig. 3). All of the completely duplicated ureter was removed at the initial operation in only four of these 24 cases.

A typical example was the patient with recurrent urinary infection and fever who had a functionless left upper segment which was visualized by retrograde pyelography (fig. 4). There was reflux up this ureter (fig. 4*b*). Only the accessible portion of ureter was removed at the time of heminephrectomy (fig. 4*c*). To date, the stump of ureter has caused no trouble. So far, only two ureteral stumps have had to be removed in this group of 20 patients that had a portion of the duplicated ureter left in situ. But admittedly all of these are not known to have reflux.

Ectopia without incontinence. Seventeen female

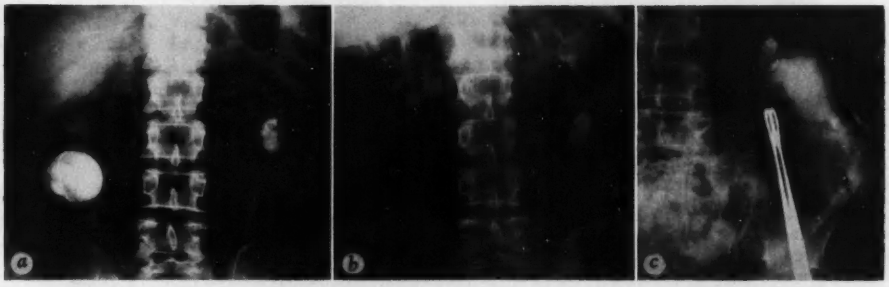

FIG. 2. Heminephrectomy. *a*, Plain roentgenogram showing calculi in lower portion of each kidney. *b*, Excretory urogram 6 years after excision of right lower segment. Note normal upper segments and remaining calculi on left. *c*, Injected left perinephric abscess cavity 3 months after incision and drainage. Note drainage tube extending to cavity in pelvis.

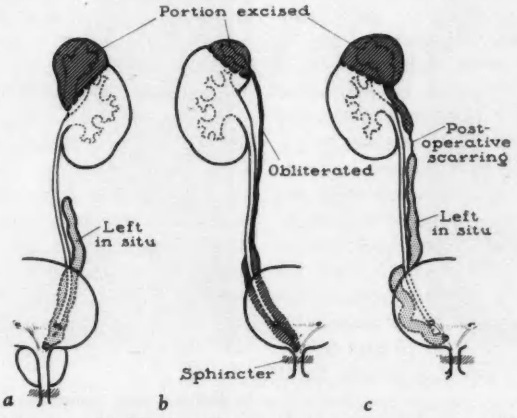

FIG. 3. Complete duplication with blind-ending ureter to upper segment. *a*, Absence of upper third of ureter. *b*, Complete obliteration of upper portion of ureter. *c*, Postoperative ureteral occlusion. Note that all ureters open intravesically and that complete heminephro-ureterectomy was performed in only 1 case.

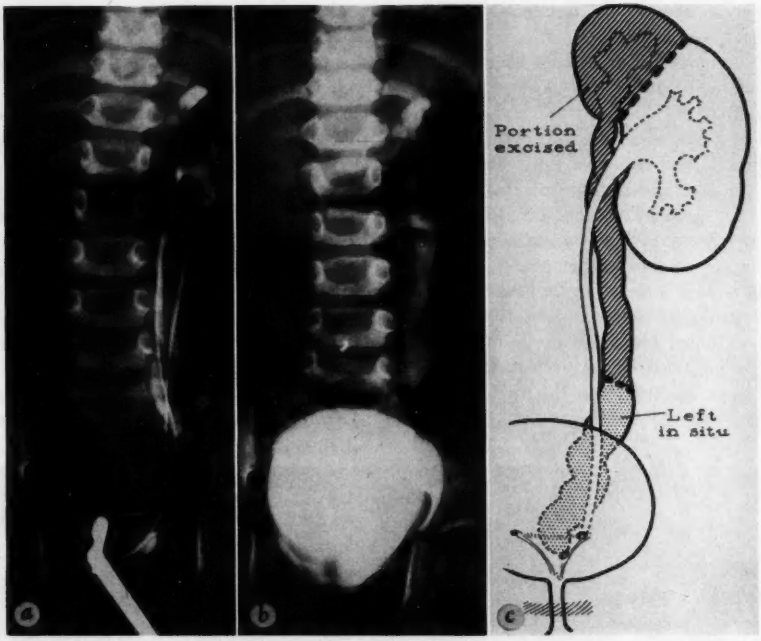

FIG. 4. Duplication without ectopia. *a*, Left retrograde pyelogram showing complete duplication of renal pelvis and ureter. *b*, Retrograde cystogram showing reflux into upper segment. *c*, Diagram of composite findings and amount of tissue removed.

patients had ectopic ureteral orifices in the urethra but inside the sphincter. For example, one child had recurrent urinary infection and a functionless upper left segment which was outlined by retrograde pyelography. After heminephrectomy and partial ureterectomy (fig. 5) the ureteral stump (fig. 5*b*) continued to be a nidus of infection and had to be removed 4 months later. The lower segment of the kidney remained normal (fig. 5*c*). Two of these 17 patients had primary complete heminephro-ureterectomy. One had no further trouble while the other eventually required removal of the remaining renal segment because of a postoperative ureteral stricture. In 10 of the other 15 cases, the ureteral stump had to be excised eventually because of persistent infection. It is conceivable that others may have to be removed later despite the fact that they have caused no trouble for at least 15 months.

There were five ectopic ureteral orifices outside the bladder in males. None of these patients was incontinent. One adult had recurrent fever, a functionless right upper calyceal system (fig. 6) and a distended right seminal vesicle. The diagnosis of ectopic ureteral orifice in the seminal tract was confirmed at operation (fig. 6*b*) and a fine specimen was obtained (fig. 6*c*), but careful dissection failed to maintain the integrity of the remaining ureter. A postoperative fistula persisted and led to severe pyelonephritis, so that the remainder of the kidney had to be removed.

Another patient lost the remainder of the kidney because of stricture after complete ureterectomy when the ectopic orifice was in the prostatic urethra. Three others were more fortunate after heminephrectomy and only partial ureterectomy. Two of these ectopic orifices were in the seminal vesicle and the third was in the prostatic urethra. None of these three ureteral stumps has caused any trouble and it is unlikely that the two excised ones would have been annoying.

Ectopia and incontinence. Few situations are more pathetic than ectopic orifices outside the urethral sphincter. These patients usually have been chastised as children and ostracized as adults. They are constantly wet with urine and

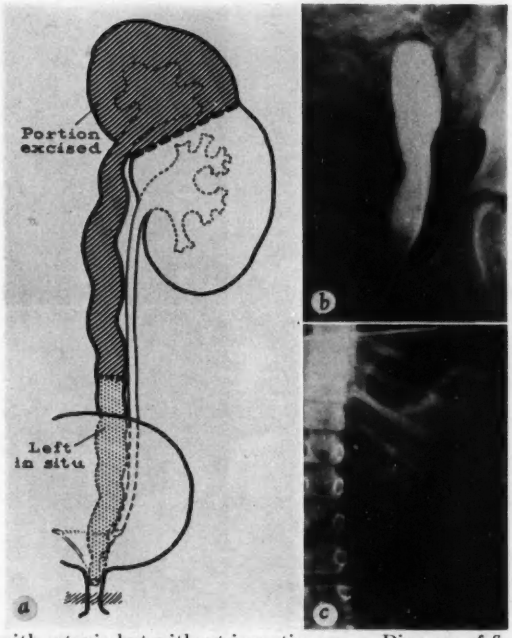

FIG. 5. Duplication with ectopia but without incontinence. *a*, Diagram of findings and initial treatment. Note ectopic ureteral orifice in posterior urethra. *b*, Retrograde visualization of infected left ureteral stump. *c*, Postoperative excretory urogram.

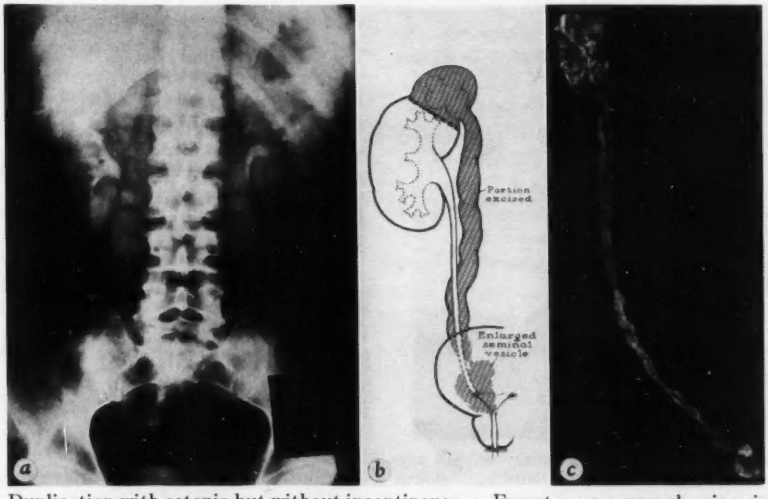

FIG. 6. Duplication with ectopia but without incontinence. *a*, Excretory urogram showing right upper pole devoid of contrast medium. *b*, Diagram of upper segment draining into right seminal vesicle. *c*, Photograph of specimen. Note communication between ureter and seminal vesicle.

still capable of urinating normal amounts at normal intervals. There were 33 such females in this series.

The guilty segment may not be obvious. For example, a woman, 28 years old, was married, wet and miserable. There was only a suggestion that the right upper pole had a calyceal deficiency (fig. 7*a*). This segment opened in the

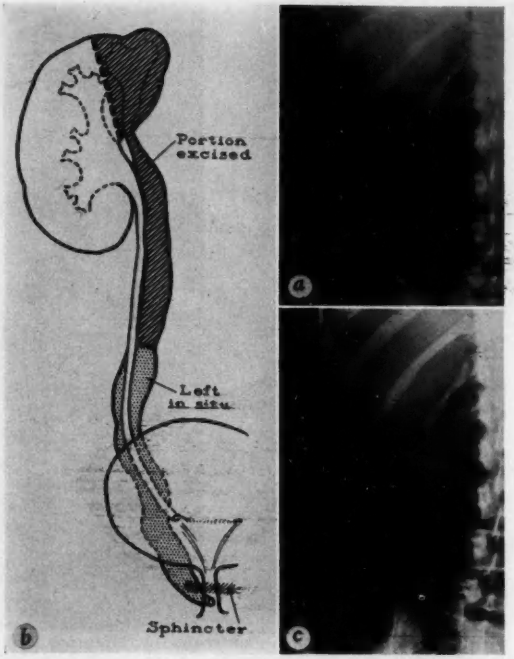

FIG. 7. Duplication with ectopia and incontinence. *a*, Excretory urogram with suggestion of calyceal defect in extreme right upper pole. *b*, Diagram of ureter opening in anterior urethra. *c*, Postoperative excretory urogram.

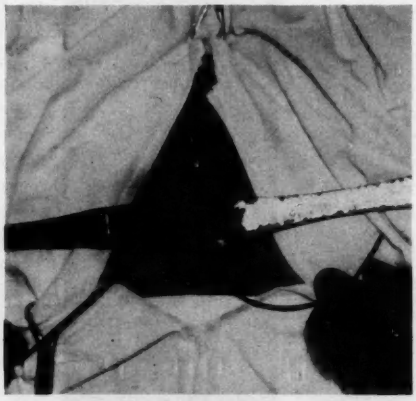

FIG. 8. Bilateral duplication with ectopia and incontinence. Note catheterized ureteral orifices outside urethral meatus.

anterior urethra (fig. 7*b*). Removal of it did not affect the remainder of the kidney (fig. 7*c*), but the urinary incontinence stopped immediately.

Two patients in this group had to have bilateral operations before they were cured. All four orifices were located preoperatively in one case (fig. 8) reported by Greene and Ferris,[1] but in the other the second operation was prompted entirely by the history of continued urinary incontinence.

TABLE 2. *Eighty-five completely duplicated ureters*

Site of extra orifice	Total	Primary ureterectomy		Stumps removed
		Complete	Partial	
Bladder	29	4	25	2
Posterior urethra				
Female	17	2	15	10
Male	2	1	1	0
Seminal vesicle	3	1	2	0
Anterior urethra or vagina	34	2	32	0
Total	85	10	75	12

[1] Greene, L. F. and Ferris, D. O.: Urinary incontinence due to bilateral ectopic ureters. Surg., Gynec. & Obst., **82**: 712–716, 1946.

Frequently the ectopic orifice is found near the urethral meatus, as shown in figure 8, although any portion of the vestibule may be the site. Surprisingly enough, one additional patient with an orifice in this location had no incontinence. She had recurrent pain and fever and a functionless left upper segment. DeWeerd and Litin[2] reported this case in detail and found five comparable ones in the literature.

Complete heminephro-ureterectomy was performed in only 2 cases in this group. The 32 remaining ureteral stumps have caused no trouble, since they open distal to the urethral sphincter.

The pertinent aspects of these observations are summarized in table 2. Five of the completely duplicated ureters were associated with calculous disease. The other 80 were operated on because of infection or incontinence.

For statistical purposes it is regrettable that the groups treated with complete and partial primary ureterectomy are not comparable. But early difficulties with the blood supply to the remaining ureter soon tempered enthusiasm for total heminephro-ureterectomy. These occurred despite what seemed to be careful dissections. Ages of the three unfortunate patients were 4, 39 and 45 years, respectively, so diminutive anatomic structures were not responsible. It is noteworthy that complete ureterectomy promised to have no therapeutic advantage over partial ureterectomy in 2 of these 3 cases.

Removal of all of the ureter at the initial operation would seem to have most value when the ectopic orifice is in the female urethra but inside the sphincter. The uretero-urethral juncture has no valvelike mechanism and the ureteral stump acquires all of the latent potentialities of a urethral diverticulum.

The fate of ureteral stumps that open intravesically varies. Although the true incidence of reflux was unknown in this study, fewer ureteral stumps have had to be excised than had been anticipated. Perhaps reflux ceased in some instances after removal of the infected renal segment.

It is significant, however, that none of 35 stumps that opened outside the urethral sphincter has been troublesome.

Even though complete ureterectomy was devoid of complications in 7 patients, one must question the wisdom of primary total heminephro-ureterectomy in *any* case. Blood supply of duplicated ureters can be notoriously variable. A two-stage operation is much safer, for it has not compromised the remaining ureter in any of 12 patients who were managed in this manner. Furthermore, secondary ureterectomy promises to be necessary in only 15 to 20 per cent of all heminephrectomies.

SUMMARY

So-called heminephrectomy can be performed safely at any age. The term should be confined to removal of one segment of a kidney with dupplication of the renal pelvis. The most common indications are calculi, infection and urinary incontinence.

Elaborate operative techniques are unnecessary. A wedge-type cortical resection and closure with mattress sutures usually will suffice. Associated nephrostomy is becoming extinct. Disposition of the corresponding ureter in cases of complete duplication poses the most controversial problem.

Heminephrectomies are subject to the same misfortunes that stalk any kind of surgical procedure, but the only special menaces are errors in the management of blood vessels. These can be minimized if one avoids primary total heminephro-ureterectomy and removes offending ureteral stumps at a second stage. This will be necessary in only 15 to 20 per cent of all cases. When the duplicated ureter opens outside the retention mechanism of the lower urinary tract, it is unlikely that residual ureter will cause trouble and primary complete ureterectomy cannot be justified.

[2] DeWeerd, J. H. and Litin, R. B.: Ectopia of ureteral orifice (vestibular) without incontinence. Proc. Staff Meet., Mayo Clin., **33**: 81–86, 1958.

DISCUSSION

DR. DONALD A. CHARNOCK (Los Angeles, Cal.): I should like to second what Dr. Culp says about removal of the ureter. Our series of cases at the Children's Hospital is not comparable in number with the series that Dr. Culp presented to you, but we have had around 20 cases in the last 10 years. Of those cases, only two and possibly a third one, which is still showing some infection, have required removal of the stump. The last case is one in which I am still trying to clear up the infection. I think these patients with double ureters, particularly those that terminate in unusual places, are very challenging to the urologist. Dr. Culp says that you can almost make this diagnosis over the telephone.

One case recently came to us from a community at some distance from our hospital. The diagnosis was literally made over the telephone. It proved to be an ectopic ureter, although we were never able to find the exit. I feel that by carrying the excision of the ureter as far down as is possible with ease under the initial incision and then waiting for a period of time, that the majority of these cases will clear of infection. If at a later date the ureteral stump has to be removed it may be done as a secondary operation.

DR. REED M. NESBIT (Ann Arbor, Mich.): I would like to ask Dr. Culp a question regarding the technique of removing the lower segment. I am prompted to make this inquiry, because I have on my hands two patients, both adults, who have a lower segment left, which is very, very large, and there is a very large stoma in the urethra. The original diagnosis was ureteral diverticulum. I have been hesitant in thinking about removal of this lower segment, because I am fearful that the patient will end up with a very large fistulous tract there if I go about it in any way I can think of. I would like to have you discuss the technique of removing this lower segment in cases of that type.

DR. CULP: I have wondered if such patients would be incontinent, but they apparently do extremely well, and the procedure is not as hazardous as one would think.

I usually use one half of a Cherney incision. The stump of the ureter is dissected down until one reaches the urethra, which is easily identified with an indwelling catheter. The urethral opening is closed with two layers of catgut sutures.

DR. NESBIT: By way of the perineum?

DR. CULP: No, from above.

A TECHNIQUE FOR POSTERIOR URETHROPLASTY

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Extensive scarring around the posterior urethra still presents an occasional problem. The majority of bulbar strictures can be treated by more conservative means, but posterior urethroplasty is sometimes indicated.

The procedure for posterior bulbar urethroplasty described below was developed as an alternative to the standard Johanson procedure with particular regard to the more posterior stricture. It was designed to provide easier access and suturing of the scrotal skin to the vertical bulbar or membranous urethra; the most important advantage however is the wide skin lined posterior perineal urethrostomy which subsequently provides easy inspection of the posterior bulbar and the membranous urethra in direct line of vision up to the bladder.

THE PRINCIPLES OF THE PROCEDURE

1) Longitudinal perineal incision exposing if necessary the lower membranous urethra.

2) Advancement of scrotal flap.

3) Urethroscrotal anastomosis.

4) Suspension of infolded skin by urethral catheter.

The resulting perineal fistula is wide and the posterior urethra is kept under direct observation for several months until it is ready for closure.

OPERATION

The first stage is covered by a suprapubic catheter inserted at least three inches above the pubis to ensure rapid closure on removal. Short term stilbestrol, started preoperatively, prevents an erection in the early postoperative period.

If the stricture is passable, a metal bougie is introduced; if not, bougies are passed to the stricture from above and below.

With the patient in the lithotomy position, the stricture is exposed through a midline incision from the posterior margin of the scrotum towards the anal margin (fig. 1, *A*).

The procedure of preference is excision of the stricture with end-to-end roof anastomosis after mobilization of the anterior bulbar urethra; if this is not possible owing to the extent of fibrosis or length of the stricture, the fibrotic peribulbar and periurethral tissues are excised. If there is no true urethral lumen in the strictured area a narrow bridge of fibrous tissue is preserved to locate the ends of the normal urethra and provide a smooth, narrow midline dorsal scar in the urethra which facilitates any subsequent instrumentation (fig. 1, *B*).

A wide flap of scrotal skin is advanced on the Y-V principle (fig. 2, *A*). The width required is at least twice the depth of the perineal wound. The anterior base of the flap should be wide to ensure adequate blood supply.

Two suitably located "buttonhole" incisions are made in the scrotal flap and the margins of these anastomosed to the ends of the normal urethra in front and behind the stricture (fig. 2, *B*).

The chromic catgut sutures anastomosing scrotal skin to the urethra are inserted individually under direct vision (fig. 3). The combination of a side-hinged, bi-valve aural speculum and a cleft palate Reverdin needle is preferred for the posterior urethral sutures (a slide controlled by the button on the handle closes the lateral eye before the suture is pulled back).

A Foley catheter passed to the bladder from the penis suspends the scrotal skin by the bridge between the buttonhole orifices; there is no tension on the flap but the Foley catheter provides an additional support to overcome the muscular elasticity of the scrotum, and the increased apposition achieved by this also helps to overcome the peculiar reluctance of affixation exhibited by the subcutaneous tissues of the scrotum (fig. 4, *A*). Laterally placed local stab drainage is used as required.

The Foley catheter is removed after 8 to 12 days (the urine is drained by suprapubic catheter for about 3 weeks until the perineum is well healed, thereafter the patient voids freely per urethrostomy until this is closed at the second stage); the scrotal bridge overlying the roof of the urethra is then incised longitudinally and the edges trimmed to expose the midline urethral roof (or the wider end-to-end roof anastomosis) (fig. 4, *B*). Failure to incise the skin bridge

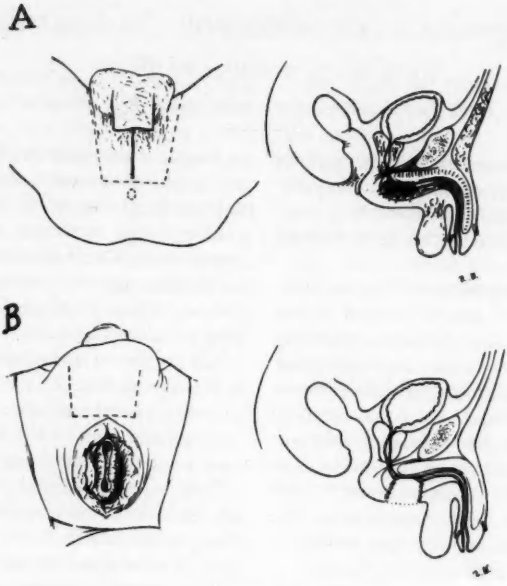

FIG. 1

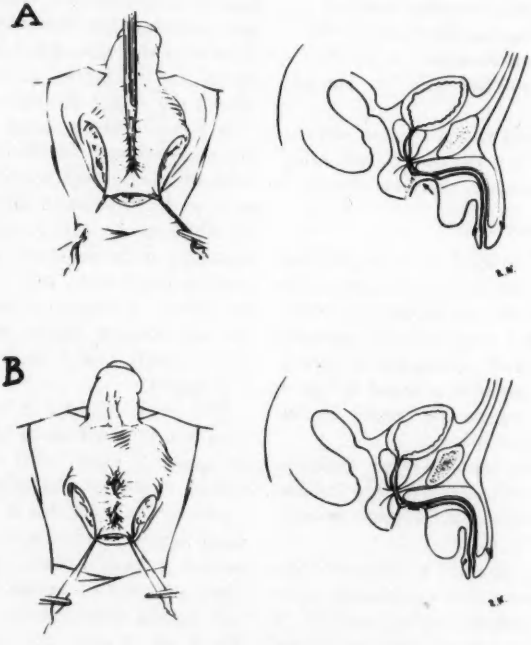

FIG. 2

and attempts to replace a segment of urethra wholly by scrotal skin without a dorsal roof scar tend to result in a hanging roof (fig. 5, *b*) and a stricture at either end (fig. 5, *a*).

The reconstructed urethra is kept under observation for at least 2 to 3 months to allow the implanted skin to achieve local blood supply. The perineal urethrostomy cannot of course close spontaneously unless there has been failure of urethroscrotal union. The membranous urethra can be inspected without difficulty in the lithotomy position by direct vision (fig. 6) and it is most important that the urethrostomy should not be closed until it is certain that there is no residual tendency to formation of stricture or "roof ridges"; any such tendency can be corrected by a minor rearrangement of skin or mucosa. Hair follicles in the area of the scrotum which forms the new urethra should be destroyed as soon as the hairs grow. An extremely fine diathermy needle is insulated by dipping in shellac and only the extreme point is then bared. The hair is held in forceps and the needle passed along the shaft for about ⅛ inch; a momentary depression of the diathermy pedal delivers a follicle-destroying burn at the point of the needle which is barely detectable from the surface (an uninsulated needle merely results in a wide surface burn). It is advisable to check the strength of the current on a relatively unimportant area of the scrotal funnels before proceeding to the important skin forming the new urethra.

When the urethra is considered satisfactory, the perineal urethrostomy is closed in the usual

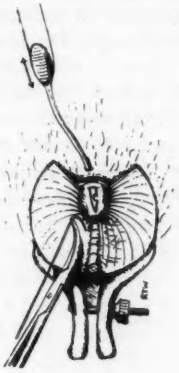

FIG. 3

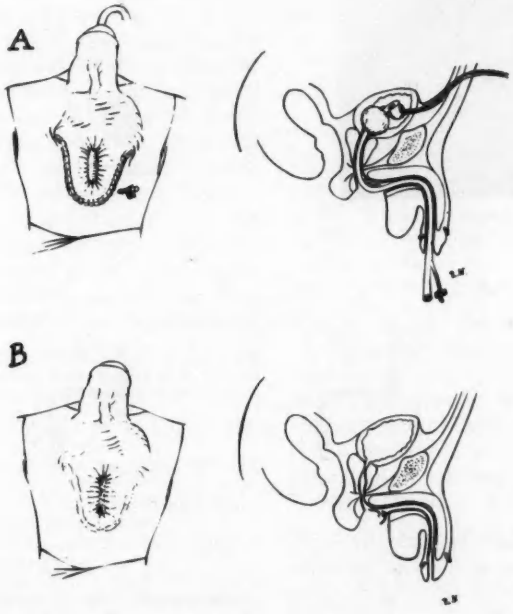

FIG. 4

manner by incision around the funnel after passage of a large bougie to enable the size of the skin remnant to be assessed (fig. 7).

If too much skin is left an immediate urethral pouch results (fig. 8, *A*). The later development of this complication is probably prevented by careful closure of the wound in layers with particular attention to the resuture of the residual bulbar and peri-bulbar tissues (fig. 7).

A minor rearrangement of the anterior and posterior ends of the implant creates a funnel-shaped urethral entry and avoids a small pouch with an eccentric urethral orifice which may subsequently catch the tip of a urethral instrument (fig. 8, *B*).

The technique just described is not necessarily contraindicated by lesser degrees of scrotal scarring if an adequate flap can be mobilized. If the perineal tissues are heavily infected at the time the patient appears, they are excised and the urethra opened, but scrotal advancement should probably be delayed until the granulating area is clean.

The anterior urethra can be opened in the usual way, if distal strictures co-exist. (In the case shown in figure 6, further strictures of the anterior urethra failed to respond to dilatation and the anterior urethra was opened ventrally throughout its length as far as the posterior urethrostomy. A further narrow Y-V flap, the width of the urethra, was fashioned from the anterior scrotum and advanced to the posterior urethrostomy to form the floor of the urethra under the base of the scrotum.

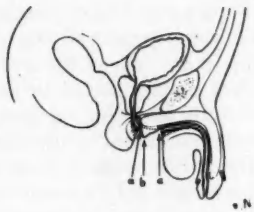

FIG. 5

FIG. 6

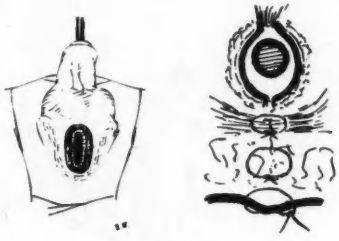

FIG. 7

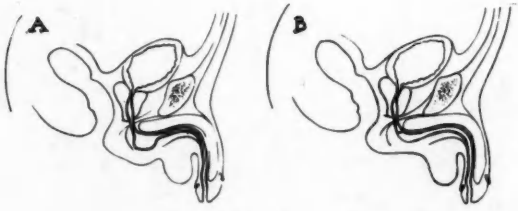

FIG. 8

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EFFECT OF DIPHENYLTHIOCARBAZONE ON PROSTATES OF ANIMALS AND IN HUMAN PROSTATIC CANCER

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Zinc is present in high concentration in the prostates of rats[1] and man.[2] Daniel, Haddad, Prout, and Whitmore[3] observed that zinc localized in the prostates of humans. Prout and Whitmore[4] have established that there is a relationship between the androgen status of dogs and zinc localization in the prostate. Mori, Nishizuka, and Midorikawa[5] have shown decreased zinc in the prostates of mice and rats treated with dithizone. Whitmore[6] has observed that a single intravenous injection of dithizone causes inhibition of prostatic secretion in dogs. Our studies, here reported, confirm the previous studies and extend them to a small series of patients.

In rats dithizone can be given by injection or orally in aqueous suspension or in oil. It is well tolerated in doses of 15 to 50 mg. per kg. in oil daily. Within a few hours of administration the urine is colored red-orange. Absorption from the gastrointestinal tract must be complete as the stools are not colored. Animals receiving the large doses show slight weight loss or failure to gain during treatment. There is a proportionality between dose and response of the prostate shown in table 1. When dithizone was given over a long period of time, except for failure to gain a normal amount of weight, the animals seemed healthy. Complete postmortem examination did not disclose unusual changes in weight or gross appearance of the endocrine glands or parenchymatous organs. Microscopic examination disclosed increased amounts of iron pigment in the liver and spleen. The testes, pituitary, thyroid, adrenals, and pancreas were microscopically normal. The retina was not abnormal. Blood counts during treatment did not show any significant change. There was significant atrophy of the prostate in all its lobes (table 2). The seminal vesicles showed atrophic changes only at higher doses. In the reconstituted prostate test of Scott, dithizone was relatively ineffective even at high doses.

In vitro the anerobic glycolysis of rat ventral prostate slices was not inhibited by dithizone, 1 mg. per ml. (table 3). Human benign prostatic

TABLE 1. *Effect of dithizone treatment in rats*

Dose	Route	Vehicle	Duration	Toxicity	Prostate, % of Control
mg./kg.			*days*		
25	oral	1% acacia	21	0	92
50	1 M	acacia	21	+	89
100	1 M	acacia	28	+	70
150	1 M	acacia	28	++	52

TABLE 2. *Chronic toxicity of dithizone in rats*

Dose	Route	Vehicle	Duration	Toxicity	Prostate, % of Control
mg./kg.			*days*		
15 daily	1 M	oil	56	0	74
50 3 × wk.	1 M	acacia	112	+	64
50 3 × wk.	1 M	acacia	168	+	52

TABLE 3. *Effect of dithizone on prostates of castrate rats receiving 1 mg. testosterone every 2 days*

Dose	Route	Vehicle	Duration	Toxicity	Prostate, % of Control
mg./kg.			*days*		
100	1 M	acacia	21	0	92
100	1 M	acacia	21	0	100
150	1 M	oil	14	0	82

Supported in part by research grants in aid CY-4334 National Cancer Institute, United States Public Health Service and T-26A from the American Cancer Society.

[1] Mawson, C. A. and Fisher, M. I.: Nature, **167:** 859, 1951.

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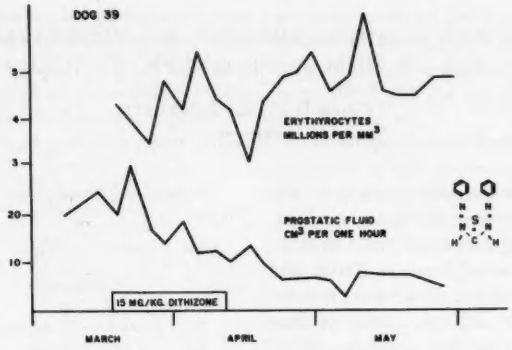

FIG. 1. Effect of dithizone treatment on secretion of dog prostate

TABLE 4. *Carcinoma of prostate with metastases treated with dithizone*

Patient, age	Previous therapy	Days of Dithizone	Results
A. V., 79	orchiectomy, stilbestrol	3	No effect, died
J. L., 43	orchiectomy, stilbestrol	5	No effect, died
G. P., 77	orchiectomy, stilbestrol	29	No effect, anemia
J. H., 76	stilbestrol	26	Good, anemia
A. E., 66	stilbestrol	12	Good, nodes decreased
R. O., 69	none	19	Good, decreased phosphatase
J. S., 57	none	10	Good, decreased "
	orchiectomy, stilbestrol	16	Slight "
J. O. S., 94	none	16	Good, decreased "

slices were inhibited from 21 to 38 per cent by concentrations of 0.1 to 1.0 mg. per ml.

In the dog prostatic secretion was inhibited promptly and for long periods of time. Figure 1 shows the prolonged effect of 2 weeks of daily administration of small doses of dithizone orally. A temporary decrease of the peripheral blood erythrocyte count was the only adverse effect noted.

Some patients selected for trial of dithizone therapy had had orchiectomy and stilbestrol treatment and were in relapse. All had tissue diagnoses and elevated specific acid phosphatases by the method of Reynolds, Lemon and Byrnes.[7] Medication was given orally, usually 1.5 gm. per day. Blood counts, serum phosphatases, glucose, blood urea nitrogen, prothrombin time, thymol turbidity, bilirubin, and body weight were determined at frequent intervals. All patients had some gastric distress relieved by

[7] Reynolds, M., Lemon, H. and Byrnes, W.: Cancer Research, **16**: 943, 1956.

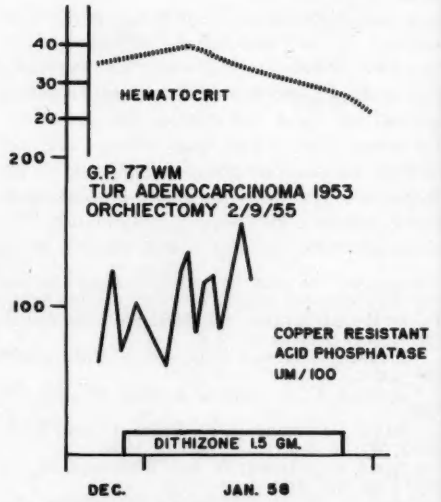

FIG. 2. Patient G. P. Adenocarcinoma of prostate treated by orchiectomy and stilbestrol 3 years prior to dithizone treatment.

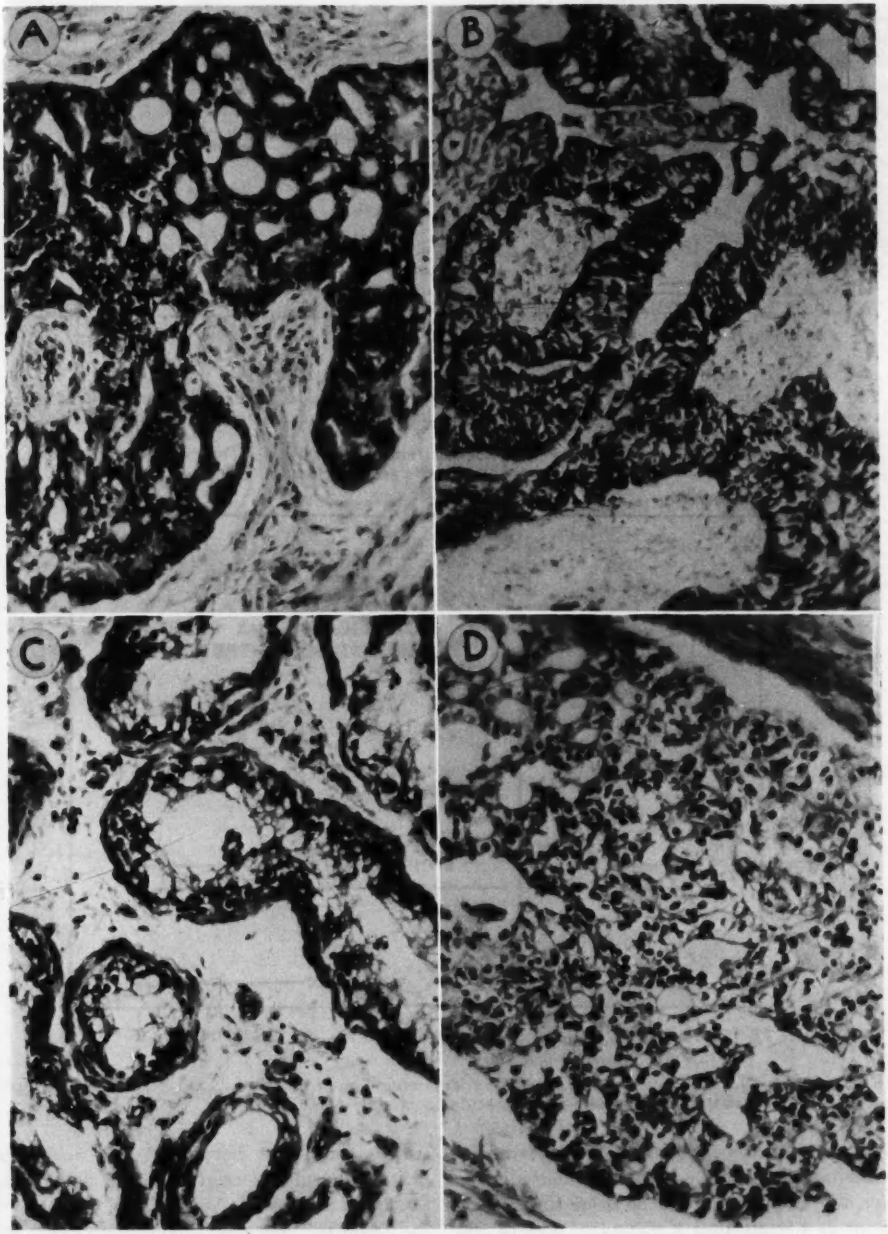

FIG. 3. Lymph node metastases before (*A* and *B*) and after (*C* and *D*) dithizone treatment. Hematoxylin and eosin for *A* and *C*, acid phosphatase stain for *B* and *D*. Regression in *C* and lack of acid phosphatase in *D* indicate effect of 2 weeks' treatment.

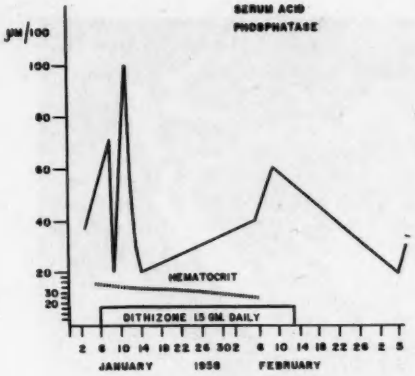

FIG. 4

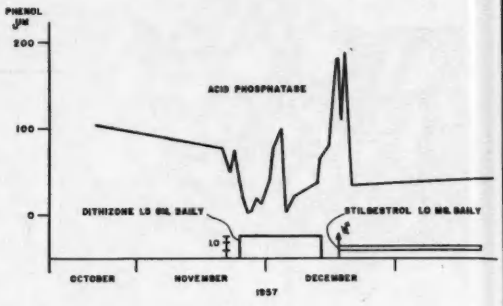

FIG. 5

FIG. 4. Patient J. H. Adenocarcinoma of prostate treated for 4 months with stilbestrol prior to dithizone. Acid phosphatases decreased and clinical improvement was noted. Anemia forced cessation of treatment.

FIG. 5. Patient R. O. Untreated metastatic adenocarcinoma of prostate. Temporary remission, clinical as well as phosphatase. Poor response to orchiectomy and stilbestrol.

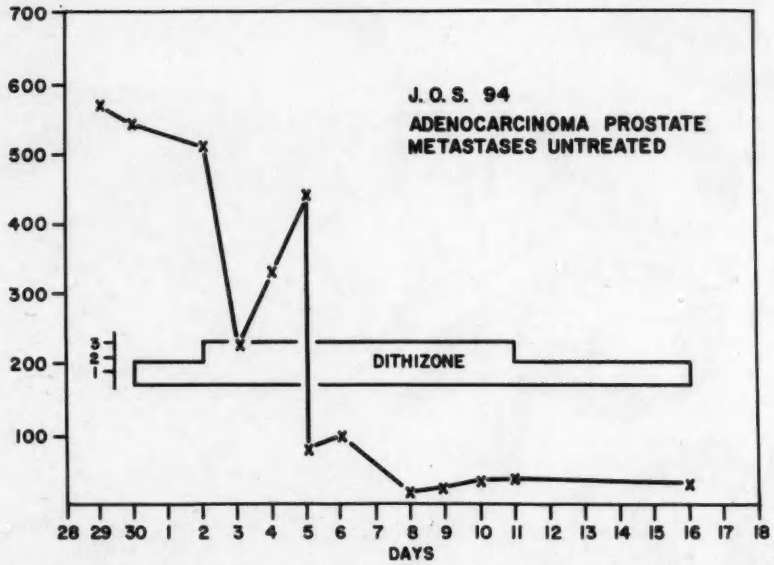

FIG. 6. Patient J. O. S. Untreated metastatic adenocarcinoma of prostate. Good clinical and phosphatase response to treatment. Died of cerebrovascular accident.

amphogel. Perhaps enteric coated tablets might have avoided this for the distress was immediately after oral administration. The urine turned red-orange in 4 hours after a single oral dose of 500 mg. The characteristic urinary color persisted for 48 hours after the last dose was given. No patient had any significant change in his laboratory studies except for hematocrit and acid phosphatase. Results of treatment of 8 patients are tabulated in table 4. None of the patients who had relapsed following orchiectomy and stilbestrol therapy showed any favorable response to treatment with dithizone (fig. 2). Two patients previously treated with stilbestrol showed evi-

dence of improvement. One patient had marked regressive changes in lymph node metastases (fig. 3). One had significant clinical and serum phosphatase remissions (fig. 4). A previously untreated patient had a better phosphatase response to dithizone than he did to orchiectomy and stilbestrol treatment (fig. 5). Another untreated patient had a good clinical and phosphatase remission (fig. 6). Two patients with benign prostatic hypertrophy were treated for 2 weeks prior to prostatectomy. No change in serum acid phosphatase values were noted but histological evidence of regressive changes were noted.

In conclusion it seems likely that dithizone treatment of patients will prove impractical because of the anemia which attends prolonged therapy. Although 5 patients of eight showed some favorable response, none of those previously treated by orchiectomy experienced a remission.

ENDOCRINE THERAPY IN CARCINOMA OF THE PROSTATE GLAND: 10-YEAR SURVIVAL STUDIES

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The indications for, and results of, endocrine treatment for carcinoma of the prostate gland still present an unsettled problem. It is only natural that this should be so, from the very character of the disease. Prostatic carcinomas vary widely in their lethal potential, and patients apparently vary greatly in their "inherent resistance" to the disease. Also, the response of such lesions to endocrine treatment has seemed quite inconsistent, unpredictable and of varying duration (Emmett and Greene, 1945 and 1946). Thus, in some cases endocrine therapy will yield dramatic palliative relief from metastatic pain (60 per cent of cases; Emmett and Greene, 1945). Only too often, however, the period of palliation is relatively short (Greene and Emmett, 1946).

This extreme variance in lethal potential of prostatic carcinoma makes difficult the evaluation of various forms of treatment. Because of this it is possible, by careful selection, to find individual patients or to collect small groups of patients with prostatic carcinoma who, although having received no endocrine therapy, in the aggregate yield survival rates which approach normal. Likewise, it is possible by careful selection to collect small groups of cases and to demonstrate either the effectiveness or ineffectiveness of endocrine therapy in increasing survival. This misleading factor of selection of cases can be obviated, therefore, only by studying a large consecutive series of cases in which the various forms of therapy have been employed. This has been the object of this study. We had hoped to obtain data which might be helpful in answering such currently troublesome questions as 1) how effective is endocrine treatment for prostatic carcinoma? 2) are survival rates significantly increased by endocrine treatment? 3) should endocrine treatment be administered early or late in the disease? 4) is there need for selection of patients for endocrine treatment? and 5) is there any preference for orchiectomy, estrogens or a combination of both?

TERMINOLOGY

The following terminology will be used: *Endocrine therapy* will mean either *estrogens* or *bilateral orchiectomy* or *both*; *stilbestrol* will mean any suitable estrogen; *orchiectomy* will indicate bilateral orchiectomy.

MATERIAL

Orchiectomy group. We have studied all cases of carcinoma of the prostate gland recorded at the Mayo Clinic in which orchiectomy was done during the 10-year period 1942 through 1951. We found 560 such cases which we have designated the *orchiectomy group*, all of which qualify for 5-year survival study; 351 (63 per cent) of them qualify for 10-year survival study. Symptoms of urinary obstruction were treated by transurethral resection whenever necessary, and this operation was performed in 391 cases (70 per cent of the group). In addition to performance of orchiectomy, stilbestrol was prescribed in approximately 50 per cent of cases.

Nonorchiectomy group. As a *comparison group* we have studied all cases at the Mayo Clinic in which transurethral resection was performed for carcinoma of the prostate gland during the 5-year period 1942 through 1946. This yielded 541 cases (approximately the same number as in the orchiectomy group). In none of these cases was orchiectomy done, but stilbestrol was prescribed in approximately 75 per cent of cases. This group we have designated *nonorchiectomy group*. All these patients qualify for both 5 and 10-year survival study.

COMPARABILITY OF GROUPS (TABLES 1 TO 10)

The total study, therefore, comprises 1101 cases of carcinoma of the prostate gland in all of which some type of surgical treatment was carried out (either transurethral resection, orchiectomy or both). Eight hundred ninety-two of the patients (351 of the orchiectomy group and all 541 of the nonorchiectomy group) were cared for during the same period (1942 through 1946). They may be considered essentially as

"consecutive" and can be used as a group when statistical data for the group as a whole are computed (tables 2, 3 and 8 to 10). As can be seen in the subsequent tables, our followup data are quite complete, because we have traced almost all patients.

When the orchiectomy group is compared with the nonorchiectomy group, the entire 1101 cases will be used for computation (541 nonorchiectomy and 560 orchiectomy; tables 1 and 4 to 7). It should be borne in mind, however, that 209 of the patients who underwent orchiectomy were treated later than the others, namely, 1946–1951, and so qualify only for 5-year survival study.

In some ways members of the two groups lend themselves well to comparison, and in other ways they do not. For instance, in both groups urinary obstruction was relieved when necessary by transurethral resection. Adequate relief of urinary obstruction, with its favorable prophylactic and therapeutic effect on urinary infection, is regarded as an important factor in prolonging life. On the other hand, few believe that enough malignant tissue is removed by this procedure to alter significantly the progress of the disease.

Conversely, certain characteristics of each group hinder accurate comparison of one with the other. For instance, as would be expected, the percentage of patients with metastasis in the orchiectomy group is high, whereas in the nonorchiectomy group it is relatively low. The reverse is true for the patients without metastasis, so that when cases in the former category are compared with cases in the latter, one is comparing a large number of cases with a smaller number.

Another possible source of error is the date from which survival is computed. Unfortunately, it is impossible to determine the time of onset of the disease. In the *nonorchiectomy group* survival has been computed from the date of transurethral resection, which usually was the date on which the diagnosis of carcinoma was first established. In the *orchiectomy group*, on the other hand, survival has been computed from the date of orchiectomy, which frequently was months or years after the diagnosis had been established. Thus, in 391 cases in which both resection and orchiectomy were done, orchiectomy was done a year or more after transurethral resection in 74 cases; in 26 of the 74 orchiectomy was done 3 years or more after transurethral resection. This would tend to diminish survival rates in the orchiectomy group. From a statistical standpoint, however, calculation of the survival rates as we have done it, outlined above, appears to be the only acceptable method available to avoid setting up an artificially selected group in which some degree of control may have been obtained from the use of estrogens or from "natural resistance" to the disease.

METHODS OF EVALUATING RESULTS OF THERAPY

Results of therapy have been evaluated solely on the basis of survival. Contact with many of our patients frequently is by letter only, and evaluation of morbidity by this means is difficult. Each patient who is dead is presumed to have died from prostatic carcinoma. Our only means of compensating for deaths from other causes is to compare survival rates among our patients with expected survival rates of normal persons of the same age group in the general population.

DATA ON STILBESTROL

We do not claim accuracy for the data concerning stilbestrol. We can state simply that stilbestrol was or was not prescribed. In many cases we do not know whether the patient continued or ceased to take the drug. Moreover, we do not know if the home physicians subsequently prescribed stilbestrol in cases in which we did not. We do know, however, that it is often difficult, especially in older patients, to make them realize the importance of adhering closely to a prescribed plan of medication; they tend to forget medication and will cease and start to take it at will. This is one of the inherent shortcomings of any long-term therapy which utilizes oral medication.

CRITERIA FOR DETERMINING PRESENCE OR ABSENCE OF METASTASIS

Our criteria for the diagnosis of metastasis in carcinoma of the prostate gland are the presence of any of the following signs or symptoms (or combination of them): 1) roentgen-ray demonstration of bony metastasis or metastasis to the fields of the lungs; 2) elevation of the serum acid phosphatase above 3.5 King and Armstrong units; 3) involved palpable lymph nodes or contiguous abdominal metastatic masses; 4) invasion of the rectum in such a way that tissue containing malignant cells can be obtained

from rectal biopsy; 5) severe prostatic and rectal pain which is not relieved by transurethral resection; 6) severe pain (usually in the back or legs) which is relieved by orchiectomy or stilbestrol, even though roentgen-ray evidence of bony metastasis is lacking. *We did not regard clinical involvement of the seminal vesicles as evidence of metastasis,* because we believe this finding is present in a high percentage of all patients seen with gross clinical carcinoma of the prostate gland.

PROOF OF CARCINOMA

Carcinoma was proved in all cases either by microscopic examination of tissue or by the subsequent development of metastasis.

SELECTION OF CASES

Almost all the patients included in this study came to the Mayo Clinic seeking relief from symptoms of either urinary obstruction or metastasis or both. (In a very small number of cases, digital rectal examination done during a routine examination resulted in observations which led to the diagnosis of prostatic carcinoma.) In a small group the prostatic tissue was considered to be benign, and only after transurethral resection was performed and the tissue examined microscopically was cancer detected. In these cases we have chosen to call the condition "occult carcinoma." They will be discussed later. The overwhelming majority of patients, however, had typical "full-blown" clinical carcinoma which had diffusely and grossly invaded the prostate gland and often the seminal vesicles.

Only cases in which either transurethral resection or orchiectomy or both were done are included in this study. Patients for whom transurethral resection was not considered necessary, and who were sent home either with the prescription of stilbestrol or without any treatment, are not included. None of the patients included in this study would have been considered suitable for radical prostatectomy.

There was no selection of patients on the basis of age or general condition. The ages according to decades are listed in table 1.

CASES EXCLUDED

In 10 cases microscopic examination of the tissue removed at resection proved to be either squamous-cell epithelioma or squamous-cell epithelioma and adenocarcinoma. We have excluded these 10 cases from the study, as well as 4 cases in which extensive carcinoma involved both the rectum and prostate gland to such a degree that it was impossible to determine the site of origin of the carcinoma.

TABLE 1. *Age distribution of 1101 patients treated for carcinoma of the prostate during the 10-year period 1942 through 1951*

Age	Nonorchiectomy		Orchiectomy	
	No.	Per cent	No.	Per cent
yr.				
40–49	4	0.7	5	0.9
50–59	35	6.5	101	18.0
60–69	211	39.0	247	44.1
70–79	242	44.7	184	32.9
80+	49	9.1	23	4.1
Total	541	100.0	560	100.0
Mean, yr.	70*		67†	

* The 5 and 10-year survival rates of a "normal" male age 70 are 73.7 and 46.4 per cent, respectively.

† The 5 and 10-year survival rates of a "normal" male age 67 are 78.6 and 54.8 per cent, respectively.

EVALUATION OF RESULTS OF TREATMENT, ALL GRADES OF LESIONS

General survival rates. The over-all survival rate, regardless of type of lesion or method of treatment, is shown in table 2. It is 32.5 per cent in the case of 5-year followup studies and 14.9 per cent in the case of 10-year followup records. In table 2 the effect of metastasis on survival may be seen. This table points up the importance in prognosis of the presence or absence of metastasis at the time of first diagnosis. Note that the survival rate of patients *without* metastasis was 45.5 per cent, compared to a survival rate of only 14.5 per cent among patients with metastasis.

Influence of grade of lesion on results. Our next step was to compare data about the *nonorchiectomy* group with data about the *orchiectomy* group, and to correlate the factors of presence or absence of metastasis and the use or nonuse of stilbestrol. The resulting data concerning endocrine treatment appeared to be inconsistent and

TABLE 2. *Five and ten-year survival rates from carcinoma of the prostate (all grades included): 892 consecutive patients treated during period 1942 through 1946*

Group	Period	Patients		Survived Beyond Indicated Period	
		Total	Traced	No.	Per cent*
	yr.				
No metastasis	5	521	506	230	45.5
	10		500	114	22.8
Metastasis	5	371	366	53	14.5
	10		364	15	4.1
Total	5	892	872	283	32.5
	10		864	129	14.9

* Based on traced patients. Inquiry as of January 1, 1957.

contradictory. It soon became apparent, however, that the difficulty arose from the grade 1 lesions (Broders' microscopic system of grading) which, for the most part, seemed to behave more like benign than malignant lesions. After these grade 1 lesions were eliminated the data became more consistent and meaningful.* For the remainder of this study, the grade 1 lesions will be considered separately. We shall therefore consider first the grade 2, 3 and 4 lesions (Broders' classification), which we shall designate "clinical" carcinomas. After these have been discussed, grade 1 carcinoma will be considered.

"CLINICAL" CARCINOMA OF THE PROSTATE GLAND (GRADE 1 LESIONS ELIMINATED)

Before we proceed with a comparison of results in the *orchiectomy* and *nonorchiectomy* groups, it would seem desirable to ascertain the over-all survival rates accompanying "clinical" carcinoma and compare them with the figures for carcinoma of the prostate gland in general (all grades included), as shown in the 892 "consecutive" cases in table 2. The 178 cases of grade 1 lesions in this group were deducted, as explained above, which leaves 714 "consecutive" cases of "clinical" carcinoma. Survival rates for the 714 patients with these lesions are shown in table 3. Note that the 5-year survival rates among patients without metastasis have decreased to 36.5 per cent but that the 5-year rates among patients with metastasis remain approximately the same (14 per cent), as compared with the rate of 14.9 per cent for patients with all grades of carcinoma of the prostate gland (table 2).

Comparison of orchiectomy and nonorchiectomy groups. In the next four tables (4 to 7) all patients treated during the entire period 1942 through 1951 are considered. Thus of the 1101 total patients encountered in the period, 190 who had grade 1 carcinoma were eliminated, leaving 911. Of these 893 were traced 5 years and 697 were traced 10 years. In table 4 survival rates are correlated with the factors of performance of orchiectomy or nonperformance of orchiectomy and the presence or absence of metastasis. The table indicates that among patients *without metastasis* for whom orchiectomy was performed the 5-year survival rate was 56.8 per cent and that the 10-year survival rate was 26.5 per cent. Such survival rates are especially striking when

TABLE 3. *Influence of metastasis on five and ten-year survival rates of 714 consecutive patients with "clinical" carcinoma* of the prostate treated from 1942 through 1946*

Clinical Carcinoma	Patients		Survived Beyond Indicated Period After Operation	
	Total	Traced for period	No.	Per cent†
5-year group				
No metastasis	359	351	128	36.5
Metastasis	355	350	49	14.0
Total	714	701	177	25.2
10-year group				
No metastasis	359	349	45	12.9
Metastasis	355	348	14	4.0
Total	714	697	59	8.5

* Total patients treated in years under consideration were 892 but the 178 with carcinoma, grade 1, were excluded.

† Based on traced patients. Inquiry as of January 1, 1957.

* The manner in which the grade 1 lesions gave a false impression of the efficacy of endocrine treatment for clinical carcinoma of the prostate gland is illustrated later on in table 6.

TABLE 4. *Five and ten-year survival rates for patients with "clinical" carcinoma of the prostate treated in the 10-year period 1942 through 1951 related to orchiectomy and metastasis**

Group	No Metastasis				Metastasis			
	Patients		Survived beyond indicated period		Patients		Survived beyond indicated period	
	Total	Traced	No.	Per cent†	Total	Traced	No.	Per cent†
5-year group								
Nonorchiectomy	310	302	99	32.8	67	65	12	18.5
Orchiectomy	82	81	46	56.8	452	445	60	13.5
10-year group								
Nonorchiectomy	310	300	32	10.7	67	63	5	7.9
Orchiectomy	49	49	13	26.5	288	285	9	3.2

* Carcinoma, grade 1; not included. Inquiry as of January 1, 1957. The 5-year group includes 911 cases (1101 cases minus 190 cases of grade 1 carcinoma) in which operation was performed in 1951 or earlier; the 10-year group includes 714 (892 minus 178 of grade 1 carcinoma) in which operation was performed in 1946 or earlier; 893 patients were traced for 5 years or more; 697 for 10 years or more.

† Based on traced patients.

compared to 5-year survival rates of only 32.8 per cent and 10-year survival rates of only 10.7 per cent in similar cases (*without metastasis*) when orchiectomy was *not* done (table 4).

The results of orchiectomy among patients *with metastasis* are disappointing, the 5-year survival rate being only 13.5 per cent and the 10-year survival rate being only 3.2 per cent, results which do not seem to be as good as those obtained for patients who did not undergo orchiectomy. These figures suggest that "early" orchiectomy is an effective form of treatment. By "early" orchiectomy we mean orchiectomy done before metastasis can be demonstrated (see Criteria for Determining Presence or Absence of Metastasis, earlier in this paper).

The question arises as to how "early" orchiectomy was performed in our cases. Of the total of 560 patients in the *orchiectomy group*, metastasis was absent from 90. All these patients underwent transurethral resection in addition to orchiectomy. Of the 90, four underwent orchiectomy before transurethral resection was done; orchiectomy was done simultaneously with, or within 1 month after, transurethral resection in 66; orchiectomy was done from 1 to 12 months after transurethral resection in 9 cases; orchiectomy was performed 1 to 2½ years after in 5 cases, and it was carried out 2½ to 7 years after transurethral resection in 6 cases.

Of the 470 patients *with metastasis*, orchiectomy only (no transurethral resection) was done for 164; in 6 cases it was done before transurethral resection; in 229 cases it was done simultaneously with, or not more than a year after, transurethral resection; in 51 cases orchiectomy was done 1 to 3 years after transurethral resection, and in 20 cases orchiectomy was done 3 years or more after transurethral resection.

The effect of stilbestrol on survival is shown in table 5. Stilbestrol, used in the *nonorchiectomy group*, appears to be effective treatment for patients with or without metastasis (the 5-year survival rate among patients without metastasis being 35.4 per cent for those receiving the hormone versus 15.4 per cent for those not receiving it). Among patients with metastasis the 5-year survival rate was 21.4 per cent for patients receiving stilbestrol versus zero for patients not receiving it.

In the *orchiectomy group*, however, stilbestrol appears to exert little, if any, effect (as 55.8 versus 58.6 per cent of the nonmetastatic group survived 5 years and 25.9 versus 27.3 per cent survived 10 years). Table 5 again emphasizes the poor survival rates in patients with metastasis. Note that if endocrine therapy is used (either stilbestrol or orchiectomy or both), the 5-year survival rate among patients with metastasis varies from only 11.6 to 21.4 per cent,

the 10-year survival rate being only 2.6 to 9.3 per cent. No patients *with* metastasis who did not receive endocrine therapy lived 5 years, but the number in this group is too small to be of statistical value.

Table 6 is similar to table 5 except that in table 6 the *grade 1 lesions have been included.* This table is included to illustrate why we separated the grade 1 lesions from those in the general study. Note in table 6 that treatment with stilbestrol seemed to be ineffective in the *non-orchiectomy group* without metastasis, and note also the abnormally high percentage of 35.1 for 10-year survivals among patients who did not

TABLE 5. *Five and ten-year survival rates of patients with "clinical" carcinoma of prostate (grade 1 eliminated) treated in the 10-year period 1942–1951 related to orchiectomy, stilbestrol and metastasis*

Group	No Metastasis				Metastasis			
	Stilbestrol		No stilbestrol		Stilbestrol		No stilbestrol	
	Traced patients	Survival	Traced patients	Survival	Traced patients	Survival	Traced patients	Survival
5-year group†								
		%*		%*		%*		%*
Nonorchiectomy	263	35.4	39	15.4	56	21.4	9	0
Orchiectomy	52	55.8	29	58.6	220	15.5	225	11.6
10-year group†								
Nonorchiectomy	261	11.5	39	5.1	54	9.3	9	0
Orchiectomy	27	25.9	22	27.3	129	3.9	156	2.6

* Based on traced patients.

† Inquiry as of January 1, 1957. The 5-year group includes 911 patients operated on in 1951 or earlier; the 10-year group includes 714 patients operated on in 1946 or earlier; 893 patients were traced for 5 years or more; 697, 10 years or more.

TABLE 6. *Five and ten-year survival rates of patients with carcinoma of prostate (all grades included): Treated in the 10-year period 1942 through 1951* related to orchiectomy, stilbestrol and metastasis*

Group	No Metastasis				Metastasis			
	Stilbestrol		No stilbestrol		Stilbestrol		No stilbestrol	
	Traced patients	Survival	Traced patients	Survival	Traced patients	Survival	Traced patients	Survival
5-year group								
		%†		%†		%†		%†
Nonorchiectomy	336	41.7	117	49.6	61	24.6	10	—
Orchiectomy	56	55.4	32	59.4	229	15.3	234	11.5
10-year group								
Nonorchiectomy	333	17.7	114	35.1	59	10.2	10	—
Orchiectomy	28	28.6	25	28.0	134	3.7	161	2.5

* Inquiry as of January 1, 1957. The 5-year group includes 1101 patients operated on in 1951 or earlier; the 10-year group includes 892 operated on in 1946 or earlier; 1075 were traced for 5 years or more; 864 for 10 years or more.

† Per cent of traced patients.

undergo orchiectomy and did not receive stilbestrol as compared with a 10-year survival rate of only 17.7 per cent among those who received stilbestrol (table 6). As will be shown later, these inconsistent data were the results of inclusion of grade 1 lesions (especially the occult carcinomas) which appear to be little affected by endocrine treatment.

Summary of results in "clinical" carcinoma. On the basis of the study thus far it would appear that the following conclusions can be drawn concerning "clinical" carcinoma of the prostate gland (table 7).

First, best results were achieved among patients for whom "early" orchiectomy was done *before metastasis appeared* (5-year survival rate of 56.8 per cent and 10-year survival rate of 26.5 per cent). Stilbestrol did not seem to improve results after orchiectomy had been done.

TABLE 7. *Influence of therapeutic procedure on the 5 and 10-year survival rates of patients with "clinical" carcinoma* of the prostate treated during the 10-year period 1942–1951*

Type of Treatment	Patients Traced	Survived 5 or More Years After Treatment	Patients Traced	Survived 10 or More Years After Treatment
		%†		%†
No metastasis				
"Early" orchiectomy (with or without stilbestrol)	81	56.8	49	26.5
"Early" stilbestrol	263	35.4	261	11.5
Transurethral resection only	39	15.4	39	5.1
Metastasis				
"Late" stilbestrol	56	21.4	54	9.3
"Late" orchiectomy (with or without stilbestrol)	445	13.5	285	3.2
Transurethral resection only	9	—	9	—
Total	893		697	

* Carcinoma, grade 1, not included. 893 were traced for 5 years or more; 697 were traced 10 years or more.

† Based on traced patients.

Second, the next-best results were secured with "early" treatment with stilbestrol started *before the appearance of demonstrable metastasis* (5-year survival rate of 35.4 per cent and 10-year survival rate of 11.5 per cent).

It is of interest that the survival rates among patients *without metastasis* who to our knowledge received no endocrine therapy were not good (5-year survival rate of 15.4 per cent and 10-year survival rate of 5.1 per cent).

Generally poor survival rates were obtained among all patients with metastasis. Endocrine therapy (either stilbestrol or orchiectomy or both) yielded 5-year survival rates of only 11.6 to 21.4 per cent, as compared to no survivals when endocrine therapy was not used.

GRADE 1 CARCINOMA OF THE PROSTATE GLAND (BRODERS' MICROSCOPIC GRADING)

Dr. Malcolm B. Dockerty, head of the Sections of Surgical Pathology at the Mayo Clinic, defines a grade 1 lesion of the prostate gland as one exhibiting the following three characteristics: 1) the prostatic acinus acquires a small lumen; 2) the lining epithelium loses its papillary infoldings, and 3) fat appears in the cytoplasm (the cytoplasm is clear). A microscopic section of a typical grade 1 lesion compared with a section from benign adenofibromatous hyperplasia is shown in figure 1.

Grade 1 carcinoma of the prostate gland has been called by some a "laboratory cancer," implying that it lacks clinical significance. There seems little doubt, however, that this lesion is a definite carcinoma, because in some cases it does metastasize. The tendency toward a "benign" clinical course no doubt is greatly influenced by the generous proportion of "occult carcinomas" found in this group of cases. Occult carcinoma will be discussed later in this paper.

Material. Of the total of 1101 cases in our study, all cases involving grade 1 lesions were set aside for special study. Microscopic slides of the tissue were re-examined in each case by Dr. Dockerty. Whenever indicated, additional tissue was fixed and sectioned for slides. Only 7 cases were found in which the original grading was changed. (Five lesions were raised to grade 2, and two were increased to grade 3.) This left for study a total of 190 cases of grade 1 carcinoma. As mentioned previously, 178 of these grade 1 lesions were included in the 892 "consecutive"

lesions treated from 1942 through 1946. We were interested in learning whether or not there were any microscopic characteristics which might set apart the lesions associated with metastasis. Consequently, the microscopic sections were divided into two groups, depending on the presence or absence of metastasis. Although armed with this knowledge, Dr. Dockerty could not establish clear-cut histopathologic criteria which would permit distinction between grade 1 carcinoma associated with metastasis and grade 1 carcinoma not associated with metastasis.

Survival data. Five-year and 10-year survival rates among the 178 consecutive patients who had grade 1 lesions (table 8) were 62.0 and 41.9 per cent, respectively. The 5-year survival rate is the same as reported previously by Thompson, in 1942, and by Pool and Thompson, in 1956. The survival rates of patients with grade 1 carcinoma may be compared with survival rates of patients with "clinical" carcinoma as shown in table 3. Although there is considerable disparity between the total numbers of patients in each group (714 versus 178) the increased 5-year and 10-year survival rates of patients with grade 1 lesions as compared with the same rates among patients with "clinical" carcinoma are striking. These findings also were mentioned by Pool and Thompson, who further showed that survival rates decline as the microscopic grade increases.

Metastasis. Metastasis was demonstrated in 16 patients (9 per cent) with grade 1 carcinoma of the prostate gland, and survival rates correlated with the presence or absence of metastasis are shown in table 8. Among patients without metastasis the high survival rates of 65.8 per cent for 5 years and 45.7 per cent for 10 years suggest the influence of occult carcinoma (see below). The importance of metastasis in the prognosis again is emphasized, even in these low-grade lesions, because among patients with metastasis the 5-year survival rate is only 25.0 per cent, and the 10-year survival rate is only 6.2 per cent.

Occult versus nonoccult lesions. We found that grade 1 lesions could be readily divided into two groups: occult and nonoccult carcinoma. In the case of occult carcinoma, the presence of prostatic malignancy was not suspected on the basis of digital rectal examination or the cystoscopic appearance of the prostate gland or on the basis of any observations made during excision of the prostatic tissue. Neither clinical nor roentgeno-

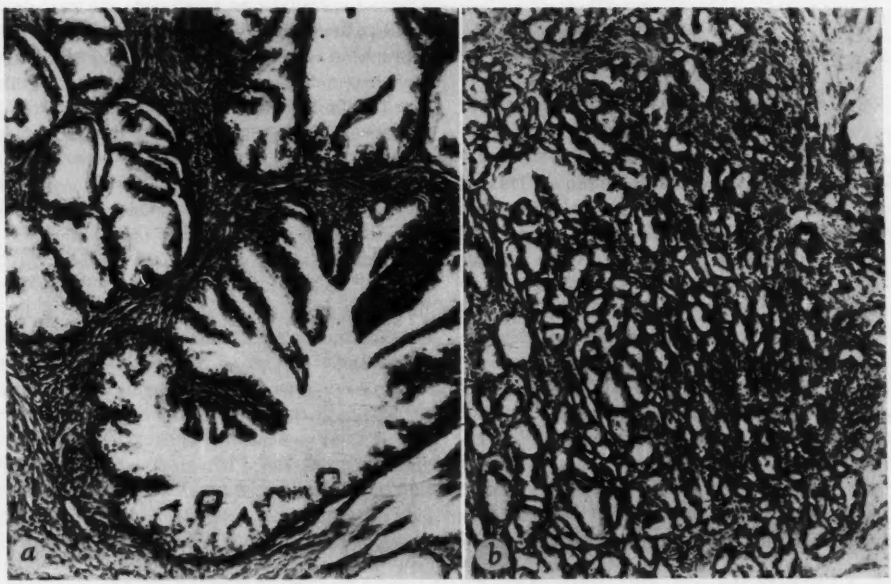

FIG. 1. *a*, Benign adenofibromatous hyperplasia (hematoxylin and eosin; ×65). *b*, Carcinoma, grade 1, of prostate gland (Broders' method; hematoxylin and eosin; ×50).

graphic evidences of metastasis were present. Phosphatase studies were not made in the majority of cases because of the lack of suspicion of carcinoma; in the few cases in which such studies were made the results were normal. In each case the diagnosis was established only by microscopic study of the tissue, and in many cases the carcinoma was found in only a few blocks of tissue. In the nonoccult grade 1 carcinomas, on the other hand, the diagnosis of malignancy was always strongly suspected on the basis of results of digital rectal examination. The characteristics of each group will now be considered separately.

TABLE 8. *Influence of metastasis on the 5 and 10-year survival rates of 178 consecutive patients with carcinoma, grade 1, of the prostate, treated from 1942 through 1946**

	Patients		Survived Beyond Indicated Period After Operation	
	Total	Traced for period	No.	Per cent†
5-year group				
No metastasis	162	155	102	65.2
Metastasis	16	16	4	25.0
Total	178	171	106	62.0
10-year group				
No metastasis	162	151	69	45.7
Metastasis	16	16	1	6.2
Total	178	167	70	41.9

* Inquiry as of January 1, 1957.
† Per cent of traced patients.

Occult carcinoma (grade 1): Of the 178 consecutive grade 1 carcinomas 112 or 63 per cent were occult carcinomas (table 9). In each case transurethral prostatic resection was performed, and in one other instance, bilateral epididymo-orchiectomy was employed for severe inflammatory disease of the testes and epididymides (rather than for endocrine purposes). Stilbestrol was prescribed for 50 patients (40 per cent) and not prescribed for the remaining 62. The 5-year and 10-year survival rates are 69.8 and 51 per cent, respectively.

These data corroborate the findings of Greene and Simon (1955) and Labess (1952). The former reported 5-year and 10-year survival rates of 71 and 39 per cent, respectively, in a series of 83 patients who had occult carcinoma; an overwhelming majority of lesions in their series were grade 1 carcinomas. Such survival rates are only slightly less than the expected rates for persons in the same age groups in the normal population (table 1). Similarly, Labess noted a 5-year survival rate of 85 per cent in a group of 33 patients with occult carcinoma treated by suprapubic enucleation. Finally, endocrine therapy does not seem to increase longevity (table 10); this finding likewise corroborates the observations of Greene and Simon. On the basis of our

TABLE 9. *Five and ten-year survival rates of 178 consecutive patients with carcinoma, grade 1, treated during the period 1942 through 1946 related to occult or nonoccult type of lesion*

Type of Carcinoma	Patients		Survived 5 or More Years After Operation		Patients		Survived 10 or More Years After Operation	
	Total	Traced	Number	Per cent*	Total	Traced	Number	Per cent*
Occult: no metastasis; 40 per cent had endocrine treatment	112	106	74	69.8	112	102	52	51.0
Nonoccult: 24.2 per cent had metastasis; 69.7 per cent had endocrine treatment	66	65	32	49.2	66	65	18	27.7
Total: 9.0 per cent had metastasis; 53 per cent had endocrine treatment	178	171	106	62.0	178	167	70	41.9

* Based on traced patients. Inquiry as of January 1, 1957.

TABLE 10. *Five and ten-year survival rates in 178 consecutive patients with carcinoma, grade 1, of prostate treated during the period 1942 through 1946 related to factors of occult or nonoccult tpye of lesion, metastasis and use or nonuse of endocrine treatment*

Type of Carcinoma	Endocrine Treatment*				No Endocrine Treatment			
	Patients		Survived 5 or more years after operation		Patients		Survived 5 or more years after operation	
	Total	Traced	Number	Per cent†	Total	Traced	Number	Per cent†
5-year group								
Occult:								
No metastasis (orchiectomy in one case)	49	46	33	71.7	63	60	41	68.3
Nonoccult:								
No metastasis	31	30	18	60.0	19	19	11	57.9
Metastasis	15	15	3	20.0	1	1	0	—
Total	95	91	54	59.3	83	80	52	65.0
10-year group								
Occult:								
No metastasis (orchiectomy in one case)	49	45	21	46.7	63	57	31	54.4
Nonoccult:								
No metastasis	31	30	10	33.3	19	19	7	36.8
Metastasis	15	15	1	6.7	1	1	0	—
Total	95	90	32	35.6	83	77	38	49.4

* Orchiectomy, estrogens or both (orchiectomy performed on only 13 patients).
† Based on traced patients. Inquiry as of January 1, 1957.

data, it would appear unnecessary to perform radical perineal prostatectomy, as suggested by others (Brendler, Hinman and Hinman, Goodwin, and Harrison and Poutasse), for occult carcinoma discovered by the microscopic examination of tissue removed by transurethral resection or conservative open prostatectomy.

Nonoccult carcinoma (grade 1): Of the 178 grade 1 lesions, 66 (37 per cent) were nonoccult carcinomas (table 9). In each instance carcinoma was suspected on the basis of digital rectal examination, and metastasis was noted in 16 cases (24.2 per cent of the group of nonoccult lesions). Transurethral prostatic resection was performed in each case, and bilateral orchiectomy in 12 cases. Of the 66 patients with nonoccult grade 1 carcinoma 46 (69.7 per cent) received some form of endocrine therapy. This may be compared with 40 per cent of patients with occult grade 1 carcinoma who received estrogenic therapy.

We were interested in determining the effectiveness of endocrine therapy in the treatment of nonoccult grade 1 carcinoma; does such treatment parallel or differ from its effect in "clinical" carcinoma? An attempt to evaluate these problems is made in table 10, in which 5-year and 10-year survival rates of patients with grade 1 carcinoma are shown. The data are arranged on the basis of occult or nonoccult lesions, the presence or absence of metastasis, and the use or nonuse of endocrine therapy. Study of these data suggests that endocrine therapy does not increase survival in patients with either occult or nonoccult carcinoma who do *not* have metastasis.

It is of interest to note that survival rates of patients with nonoccult grade 1 carcinoma *without* metastasis, regardless of whether endocrine therapy is or is not employed, are somewhat better than the best results obtained in our cases of "clinical" carcinoma *without* metastasis treated

by early orchiectomy (table 7). This is a little surprising when it is recalled that in Huggins' original work he felt that the reason estrogens should be effective was that the cells of many cancers of the prostate gland were well differentiated and resembled normal prostatic cells which are dependent on a constant supply of androgen. It is impossible to determine from table 10 whether endocrine therapy is effective in the grade 1 lesions *with* metastasis, because all lesions except one were so treated, leaving no group for comparison. However, the 5-year survival rate of only 20 per cent after endocrine therapy suggests very little therapeutic effect, as it compares with the poor results of endocrine therapy in the "clinical" carcinoma group with metastasis. Here again is support for the statement made previously that late endocrine therapy (after metastasis has appeared) seems to offer little in the way of any substantial prolongation of life.

COMPARISON OF ENDOCRINE AND OTHER TYPES OF THERAPY

After examination of the foregoing study the reader who has not currently reviewed the subject may still question whether endocrine treatment offers significant improvement over other types of treatment, both past and present. To enable the reader to obtain a better perspective of the subject, a brief review of a few selected published experiences pertinent to the problem may be helpful. Moreover, it may be helpful for orientation to know the expected survival rates of normal males in the general population of the age group under discussion. As shown in table 1, the expected 5 and 10-year survival rates for a male 67 years old are 78.6 and 54.8 per cent; for a male 70 years old they are 73.7 and 46.4 per cent.

Results of therapy in "pre-endocrine era." Huggins announced the results of his work which started the endocrine treatment of prostatic carcinoma in the fall of 1941 (a, b and c). The most widely quoted series of patients treated before 1941 is that of Nesbit and Plumb (1946). This series has been widely called the "control group" when attempts are made to assess the value of endocrine therapy. Of 504 traced patients cared for between 1925 and 1940, metastasis was present at the time of the first diagnosis in 231 and absent in 273. Nesbit and Plumb reported a 5-year survival rate of 6 per cent among patients with metastasis and a 5-year survival rate of 10 per cent for patients who did not have metastasis. Vest and Frazier's "control group" (1946) also is widely mentioned. It consists of 74 patients treated between 1930 and 1941. Vest and Frazier reported a 5-year survival rate of only 6 per cent.

Pool and Thompson (1956) reported on the "pre-endocrine" era results of patients of the Mayo Clinic as follows: among 349 patients for whom transurethral resection was performed between 1926 and 1936, the 5-year survival rate was 13.8 per cent; among 562 patients treated between 1937 and 1941, the 5-year survival rate was 27.1 per cent. They pointed out that improved general treatment, including the perfection of transurethral resection to eliminate urinary obstruction and infection, had substantially increased survival rates even before endocrine therapy was introduced.

Results with endocrine therapy. The first sizable group of patients studied for whom endocrine therapy was used was the "pooled series" reported by Nesbit and Baum (1950). Of 587 traced patients who qualified for 5-year survival study, the results are as depicted in table 11.

Barnes (1953) reported upon 31 patients in whom palpable nodules of the type "suitable for radical prostatectomy" were treated with estrogens only, and the 5 and 10-year survival rates in this series were 53 and 22 per cent, respectively. All lesions were proved to be carcinoma by subsequent transurethral resection or the development of metastasis.

Radioactive gold. Flocks' (1959) first 5-year survival study of patients treated by the injection of radioactive gold includes 135 traced patients. All were without metastasis, were

TABLE 11. *Five-year survival rates in Nesbit and Baum (1950) "pooled series" of prostatic carcinoma*

	% 5-Year Survival in:	
	All cases	Cases without metastasis
Stilbestrol only	18.3	29.0
Orchiectomy only	26.2	31.2
Orchiectomy and stilbestrol	36.3	43.6

TABLE 12. *Five and ten-year survivals from radical prostatectomy for carcinoma of the prostate without metastasis*

Author	Entire Group		Grossly Confined to Prostate		Microscopically Confined	
	No.	Survival	No.	Survival	No.	Survival
5-year survival						
		%		%		%
Jewett (1954)	127	48.0	79	61.0	41	
Turner and Belt (1957)	131	59.0	76	55.2	42	76.0
Twinem and Davalos (1949)	48	55.0				
Hinman (1948)	23	56.5				
Colby (1947)	34	55.0				
10-year survival						
Jewett (1954)	127	25.0	79	37.0	41	49.0
Turner and Belt (1957)	68	21.0	35	34.0	17	47.0

less than 75 years old and were in reasonably good condition. They should compare roughly with our patients who had "clinical" carcinoma without metastasis. The 5-year survival rate was 34 per cent.

Radical prostatectomy. Patients considered suitable for radical perineal prostatectomy are those who have palpable nodules which the examiner believes are confined within the prostatic capsule. As has been pointed out, however, most reported series of radical prostatectomies include some cases in which the condition is borderline. Table 12 shows the 5-year and 10-year survival rates in several series of cases divided into three groups: 1) the "entire group"; 2) cases in which the digital rectal examination suggested that the lesion was grossly confined within the prostatic capsule ("grossly confined" group), and 3) cases in which microscopic examination of the removed specimen showed the lesion to be confined within the capsule ("microscopically confined" group). An attempt to compare cases in these series with any group of cases in our study is impossible because of the marked differences in types of cases. There were no patients with early asymptomatic palpable nodules which would be considered suitable for radical prostatectomy in our series. Any such patients seen at the Mayo Clinic during the "era" under discussion either would have received no treatment or oral estrogens only. Note that the 5-year survival rates among patients who underwent radical prostatectomy in the "entire" group and in the "grossly confined" group vary from 48 to 61 per cent. The 10-year survival rates in the same two categories vary from 21 to 37 per cent. The survival rates for the "microscopically confined" group are considerably higher (5-year survival rate of 76 per cent and 10-year survival rates of 47 and 49 per cent). There has been considerable discussion as to whether or not these cases can be compared with cases of "occult" carcinoma.

Radical prostatectomy plus endocrine therapy. Scott (1957) has reported a small series of 29 patients who had carcinoma of the prostate gland without distant metastasis, but in whom the lesion as palpated rectally was definitely too advanced to be considered suitable for radical prostatectomy alone. He has treated these patients by combined radical prostatectomy and endocrine therapy (preferably orchiectomy). The 5-year survival rate is 68.9 per cent. It will be interesting to see if such favorable results can be maintained in a larger series.

SUMMARY AND CONCLUSIONS

It is apparent that a separate consideration of grade 1 carcinoma (Broders' classification) and "clinical carcinoma" (grades 2, 3 and 4, Broders' classification) is desirable, because our data indicate that survival rates among patients with grade 1 carcinoma, regardless of size or extent of the lesion, are superior to survival rates among those who have "clinical" carcinoma. Several factors probably are responsible for the favorable prognosis when grade 1 carcinoma is at hand. It has already been pointed out that 60 per cent of patients with grade 1 carcinoma, irrespective of the size or extent of the lesion, survive 5 years or more. When occult carcinoma (which in most cases is grade 1) is present, survival closely approaches normal survival rates. It is possible that occult carcinoma originates in periurethral glands, and certainly there is no reason why periurethral glandular epithelium should be immune to malignant change. It is conceivable that the biologic potential of such occult prostatic carcinoma may be of lower

magnitude than that of those carcinomas which can be detected by rectal palpation.

The prognosis for patients who had grade 1 carcinoma, the diagnosis of which was suspected by digital rectal examination (nonoccult) and which was not accompanied by metastasis, was good and did not seem to be significantly influenced by stilbestrol therapy. In 9 per cent of the patients who had grade 1 lesions in this study, however, metastasis could be demonstrated and the prognosis for these patients was poor. We were unable to assess the value of endocrine treatment in such patients, since all patients in this small group, except one, received endocrine therapy.

In respect to "clinical carcinoma" (grades 2, 3 and 4, Broders' classification), our data indicate that the best survival rates were obtained among patients without metastasis in whom "early" orchiectomy was done (a 5-year survival rate of 56.8 per cent and a 10-year survival rate of 26.5 per cent). The use of stilbestrol did not appear to increase survival rates among patients for whom orchiectomy had been done. Next best results were achieved among patients without metastasis to whom stilbestrol was administered "early" (a 35.4 per cent 5-year survival rate and an 11.5 per cent 10-year survival rate). Unsatisfactory results were obtained among patients without metastasis who did not, to our knowledge, receive endocrine therapy (transurethral resection only being done). The 5 and 10-year survival rates in this group were only 15.4 and 5.1 per cent, respectively.

The effect of endocrine treatment for "clinical carcinoma" in patients with metastasis was generally poor. That this type of treatment probably exerted some effect is indicated by the fact that 5-year survival rates varied from 11.6 to 21.4 per cent, which is somewhat higher than the 5-year survival rate of 15.4 per cent among patients without metastasis to whom no known endocrine therapy was administered. We are unable to state what the survival rate would have been among patients with metastasis if endocrine therapy had not been given, because there were only nine such patients in our entire study. None of these survived 5 years.

Cursory examination of our data might suggest that we should be able to answer the question, "Should endocrine therapy be administered 'early' or 'late' in the course of the disease?" We do not believe that we can give an unequivocal answer to this question. We do have evidence of the effectiveness of "early" endocrine therapy in patients without metastasis. We have evidence of the ineffectiveness of withholding endocrine therapy from patients seen before metastasis can be demonstrated. We have, furthermore, evidence of the ineffectiveness of "late" endocrine therapy in patients who have metastasis. However, we believe that before we can give a completely documented answer to this question our data should be compared with data from a sizable group of patients seen "early" in the course of the disease (before metastasis can be demonstrated) from whom endocrine therapy was deliberately withheld and then was administered only when metastasis occurred. Thus far such a group of patients is unavailable.

Until such additional information is available, our decisions will perforce be dictated on the basis of the available data. Our study indicates that survival of patients without metastasis is significantly increased by the early administration of endocrine therapy, and that orchiectomy is superior to the use of stilbestrol; furthermore, our study suggests that the survival rates among patients with metastasis, although they probably are increased by endocrine therapy, remain exceedingly poor. Therefore, it would not seem prudent to delay endocrine treatment until metastasis appears because of the comparative ineffectiveness of endocrine therapy after such extension has developed.

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TREATMENT OF CARCINOMA OF THE PROSTATE BY INTERSTITIAL IRRADIATION WITH RADIOACTIVE GOLD. EXPERIMENTAL AND CLINICAL STUDIES

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At the present time less than five per cent of patients with carcinoma of the prostate gland are seen early enough in the course of their disease to warrant the performance of total prostatectomy in the hope of a lasting cure. Androgen-control therapy in the form of estrogen administration, with or without bilateral orchiectomy, has enabled us to temporarily arrest the disease by bringing about varying periods of regression. In spite of this we must look constantly for additional therapeutic measures which might increase our ability to control or arrest this neoplasm.

In 1952, Flocks and Kerr first suggested the treatment of carcinoma of the prostate with interstitial irradiation by the means of radioactive colloidal gold injections.[1]

After observing the clinical work of Dr. Flocks at Iowa City, we felt that additional experimental work should be done to clarify the distribution and excretion of the radiocolloids following injection into the prostate of the dog. On the basis of these animal experiments, already published, we have shown that radioactive gold, phosphorus and yttrium are all apparently safe to use without danger to distant organs, and that all three materials are capable of destroying normal and carcinomatous prostatic tissue as well as some regional lymphatic tissue (table 1).[2, 3, 4]

In addition we have shown that destruction of tissue with any radioactive material depends chiefly upon uniform distribution of the radioactive colloid throughout the prostatic mass. This is due to the fact that the effective range of tissue destruction by the beta rays is only a few millimeters. Very complete distribution is necessary in order that the radiation will be sufficient to destroy all the tissue in a given area. Our animal studies indicated that by the accepted methods of injection, using multiple needles suprapubically with a rachet type, pressure syringe, and the addition of the spreading agent, hyaluronidase, distribution was not uniform. Large areas of normal tissue persisted within other areas of radiation scar (fig. 1).

After a carefully planned experimental study, which included not only the use of radioactive gold (Au^{198}) but also chromic phosphate (P^{32}), and yttrium chloride (Yt^{90}), we applied the injection of radioactive materials in patients with carcinoma of the prostate at Chicago Wesley Memorial Hospital and the Veterans Administration Research Hospital in Chicago.[5]

At first we injected the prostate through an open operative incision retropubically (Cherney) but later decided that this extensive surgical procedure offered no great advantage to the simple perineal injection using multiple needles (fig. 2).

In addition to the usual routine laboratory studies at Wesley Hospital, it was possible at the Veterans Hospital with the Radio-Isotope Laboratory to study urinary excretion of radioactive substance daily for the first five days following injection. Blood samples were drawn at one minute intervals for the first ten minutes following injection, and regularly thereafter for eight hours, to determine blood levels of the isotope.

Liver function tests were done preoperatively and perineal punch biopsy, blood counts and skeletal surveys were routine.

Table 2 shows typical excretion studies after

This work was made possible, in part, by funds from the Urologic Research Fund of Chicago Wesley Memorial Hospital.

[1] Flocks, R. H. and Kerr, H. D.: J. Urol., **68:** 510–522, 1952.

[2] Cooper, J.A.D., Bulkley, G. J. and O'Conor, V. J.: J. Urol., **71:** 624–627, 1954.

[3] Bulkley, G. J., Cooper, J.A.D. and O'Conor, V. J.: Trans. Am. Assn. Genito-Urin. Surg., **45:** 57–65, 1953.

[4] Bulkley, G. J., Cooper, J.A.D. and O'Conor, V. J.: Surg., Gynec. & Obst., **100:** 405–408, 1955.

[5] Bulkley, G. J., Cooper, J.A.D. and O'Conor, V. J.: J. Urol., **75:** 837–845, 1956.

TABLE 1. *Distribution of radioactive colloidal gold following intraprostatic injection in the dog*

Organ	Colloidal Gold	
	% per gram	% in total organ
Prostate	1.154	10.5
Liver	.035	14.2
Spleen	.005	0.2
Lung	.002	0.2
Kidney	.003	0.2
Bladder	.001	0.02
Marrow		
Lymph nodes	3.60	

injection of radioactive gold in the treatment of carcinoma of the prostate.

The urinary excretion of radioisotopes after intraprostatic injection in patients is quite variable, but occurs in greater part during the first 24 hours. This parallels the results previously reported in animal studies.[2, 3] Considerable radioisotopic material apparently enters the bladder and urethra at the time of injection. This is true whether the injection is done by a closed or open method.

In our later experience we increased the original concentration of radioisotopic solution from 2 to 4 millicuries per cubic centimeter to 15 to 25 millicuries per cubic centimeter, as suggested by Flocks. In spite of this, autopsy reports on patients who had received even repeated injections of radioactive gold revealed very patchy and incomplete local tumor destruction.

A careful followup study was made, embracing 42 patients with carcinoma of the prostate treated during the years 1953 through 1957, by means of intraprostatic injection of radioactive gold. This is not a large series of patients but is of sufficient size to allow some significant conclusions. Fifty-three injections were made in these 42 patients. Three patients were injected 3 times and 5 patients were injected twice. Multiple injections may help in controlling the extent of local tumor mass but failed to produce a negative post-injection biopsy in all but one patient.

Of the group of 42 patients studied, two were lost to followup, leaving 40 patients who could be included in this study. One-half of the 40 patients are still alive and the other half have died (table 3). Nineteen patients have died from prostatic carcinoma and one of coronary artery occlusion. Critical study suggests that 3 patients in this fatal group received some temporary benefit from the injection, consisting chiefly of a shrinkage of the tumor mass and less obstructive symptoms and less bleeding. The others in this group did not seem to receive significant palliation from the injected gold.

Of the 20 living patients, three had no significant change following radioactive gold injection and have actively progressive carcinoma. Seventeen patients are alive and have benefited from therapy by palpable softening of the tumor mass. Ten patients had only a temporary softening with decrease in size and hardness of the tumor mass for a period averaging one year and followed by return of palpable carcinoma. Three of these 10 had positive needle biopsy and others have not had biopsy, but we feel certain it would yield a positive result. All of this group received estrogen therapy and eight had orchiectomy. Since most of this group had no particular symptoms from their prostatic carcinoma, the benefit from gold injection was chiefly objective (palpatory) rather than subjective.

Seven patients still are alive and well and have no evidence of prostatic carcinoma. Two of this group have a negative needle biopsy, one 5 years after injection and one 2 years after injection. One patient in this group had an early localized nodule which disappeared and, after 4 years, is no longer palpable. Although no post-injection biopsy has been possible, his carcinoma may be completely controlled. All of these 7 patients have had estrogen therapy and four underwent orchiectomy (table 4).

Because we did not feel justified in withholding any possible beneficial therapy, all of our patients have received estrogen therapy and almost half of the entire group underwent orchiectomy. This makes evaluation of the results from radioactive gold alone very difficult or impossible. Critical study of the entire group suggests that of the 20 who died, only three received temporary palliation. Of the 20 living patients, 17 probably did have some benefit from injection. In 10 instances this benefit was of short duration and in seven the improvement and absence of palpable tumor persisted for a significant period of time.

DISCUSSION

We believe that the idea of achieving any significant palliation or control of extensive local

disease with radioactive gold injected intraprostatically is not supported by the foregoing figures. The best results have been observed in those patients with well localized prostatic carcinoma of small total mass, which may be more completely irradiated by the gold and potentially even be completely destroyed. Our initial animal studies of distribution would seem to confirm that the situation following injection of the carcinomatous prostate also involves incomplete distribution and destruction followed by rapid regrowth of neoplasm, and that the larger the area of attempted irradiation, the more incomplete the result. Perhaps this method of therapy will find its place chiefly in the treatment of smaller localized areas of carcinoma or in those patients who refuse, or have some contraindication to total prostatovesiculectomy. On

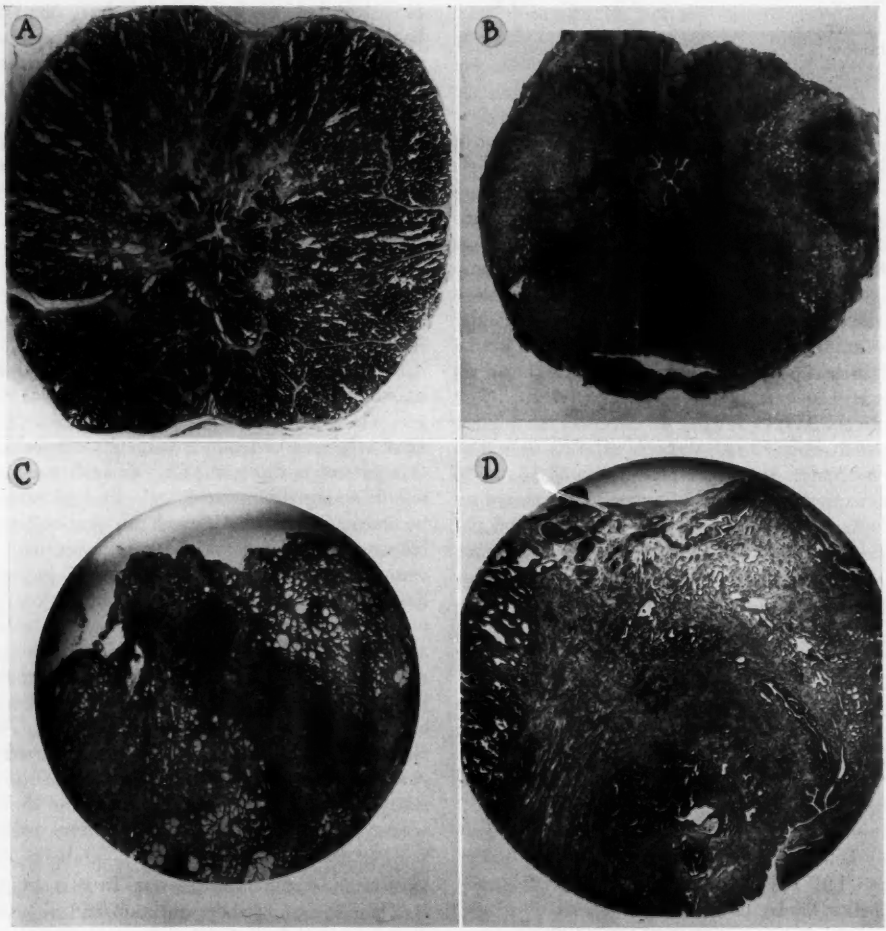

FIG. 1. *A*, normal dog prostate gland. *B*, dog prostate 3 weeks following injection of Au ^{198}. Note acute radiation reaction involving most of gland but persistence of some normal gland. *C*, dog prostate 4 weeks after radioactive gold injection. Radiation reaction is definitely limited to "path" along needle tract with little evidence of any effect beyond. *D*, dog prostate 3 months after radioactive gold injection. Section shows area of scar and persistent normal glands within and surrounding destroyed prostatic tissue.

FIG. 2. *A*, method of placing needles into prostate, guided by finger in rectum. *B*, injection of radioactive gold through needles using leaded syringe.

the other hand, perhaps these small areas of tumor represent biologically inactive tumor.

At the present time we have no evidence that radioactive gold therapy appreciably increases the survival time of patients with carcinoma of the prostate. Five year survival statistics of comparable groups of patients published by several authors,[6, 7, 8] when compared with those of Flocks[9] do not show any significant difference. Our experience would bear this out and, therefore, we do not believe that this method of treatment should be applied with the idea of prolonging life or effecting a cure, although in highly selected cases such may be possible.

If radioactive gold therapy does not seem to appreciably increase survival, does it cause sufficient palliation to be worthwhile? We believe that in isolated instances the answer is "yes," but that these instances are rare. Again, in carefully selected patients with localized areas of carcinoma the palliative effect may be very worthwhile. The evaluation of such a method of treatment is extremely difficult due to many variables in the activity of neoplasm, interpretation of results, and lack of adequate control studies. After reviewing our experimental and clinical studies as well as those of other authors, we believe that this method of treatment is not sufficiently promising or logical to warrant widespread use and that further application should be

TABLE 2

Patient	% Administered Dose Excreted in Urine			Max. Circulating Blood Content, % Dose
	1st day	2nd day	3rd day	
		Au^{198}		
R. J.	.06	2.50	0.05	
C. H.	38.49	0.10	0.03	
F. Z.	35.90	.17	.07	
C. R.	37.87	1.19	1.36	9.7
C. G.	11.33	0.60	.030	11.3
C. H.	14.40	0.17	0.06	

TABLE 3. *Followup study*

Total patients	42
Total injections	53
Lost to followup	2
Living	20
Dead	20

TABLE 4. *Surviving patients*

No benefit	3
Temporary softening	10
No palpable tumor	7
Total	20

[6] Nesbit, R. M. and Baum, W. C.: J. A. M. A., **143:** 1317, 1950.

[7] Ganem, E. J.: New Eng. J. Med., **254:** 1086–1087, 1956.

[8] Pool, T. L. and Thompson, G. J.: J. A. M. A., **160:** 833–837, 1956.

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confined to highly selected patients and carried out only under carefully controlled conditions.

SUMMARY

A review of experimental studies following injection of radioactive gold into the canine prostate shows that it is impossible to completely irradiate the gland because of poor distribution of the colloidal solution.

Loss of injected radioactive material into the bladder and urethra, as well as into the bloodstream and thence to distant organs, leaves about 10 per cent of the total injected dose acting directly on the prostate, following injection into the dog's prostate. A comparable percentage seems likely in the human from figures of blood and urine losses in patients following radioactive gold injection into the carcinomatous prostate.

A group of 40 patients receiving intraprostatic radioactive gold has been carefully followed. Only seven of this group seemed to have significant palliative effects from irradiation.

Complete control of carcinoma of the prostate by this method of treatment seems highly improbable.

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DISCUSSION

DR. WILLIAM HERBST, JR. (Washington, D. C.): I want to express appreciation and gratitude for these brilliant contributions to our complex problem of therapy for inoperable cancer of the prostate.

I should like to comment on various aspects of what has been presented and suggest, maybe, several other methods of therapy when those already instituted prove ineffective.

First of all, in regard to P-32. Quite some few years ago, Mathes at the Naval Medical Center used P-32 not as a therapeutic agent but as a diagnostic agent to assist in demonstrating osteometastases, which at that stage, were not demonstrable by x-ray films. He used P-32 intravenously, and by using Geiger counters, was able to demonstrate to his satisfaction the location of osteometastasis by means of the Geiger counter. I did observe, interestingly enough, in light of what has been said, that one or two of those patients in whom he used his method of diagnosis actually had some clinical relief of pain.

In regard to other methods, the admission of cortisone or any of the antiphlogistic steroids is a beneficial pleasing therapeutic agent in so far as relief of pain is concerned. How valuable this method of treatment is, in so far as the extension of life expectancy is concerned, we have no reliable data at this time. Nitrogen mustard is another agent which, in rare instances, seems to be effective in relieving pain and favorably modifying and influencing the clinical trend.

In so far as the pituitary problem is concerned, many years ago, Dr. Sauer of Buffalo stated that he used pituitary radiation routinely in the management of all inoperable malignant prostatic cases and said that his experience was to the effect that about 85 per cent of those patients were favorably influenced. I reported pituitary irradiation in 1943.

We have quite a few methods of attacking the pituitary aspect of this problem. We have just ordinary radiation. We have insertion of radon seeds, surgical removal, and, of course, Lawrence demonstrated as satisfactorily as any of us should demand with the betatron, how to totally and completely destroy the pituitary gland.

We have all these methods in the management of these patients. Huggins established percentage-wise the potential effectiveness of adrenalectomy which he estimated to be 20 per cent. In spite of the fact that most of the large medical centers today refuse to do adrenalectomy even if the patient and the family demand it, it seems to me that when the patient and the family request and demand adrenalectomy, it should be carried out.

In so far as Dr. McDonald's paper was concerned, it would appear that if zinc seems to be concentrated in the prostate, it might be the basis for some energetic, ambitious research person to attempt to hook on some radioactive material to zinc, inject that, and use that, maybe, as a method of treatment also, to add onto what we already have available.

Before concluding, there is one philosophical comment I would like to make in so far as the management of patients with inoperable cancer of the prostate is concerned; namely, that when one or the other, or several types of therapy are utilized without success, that is no justification whatsoever for the physician, who is responsible for the management of the patient, not utilizing, and substituting types of treatment, which, percentage-wise, may not seem to be too attractive, but yet have some possible chance of being effective.

One other thing I would like to say, which I forgot. It relates to krebiozen. Because Ivy saw fit to introduce it in a very unethical way, because the American Medical Association has frowned on it, as has the American Cancer Society, there is no justification, in my opinion, for any physician to refuse to use krebiozen when and if the patient wants it and he is willing to use it.

Without going into any great detail in so far as krebiozen is concerned, I know of one instance of a doctor, a friend of mine in Washington, who had the benefit of castration and estrogens and was bedridden and going downhill, becoming rehabilitated with krebiozen and going back to his office and engaging in his surgical practice for a month.

I know of other cases which time doesn't permit going into detail about, but, philosophically, again, I don't think it is justifiable to cease and desist in the management of any patient with

prostatic carcinoma because you have seen fit to utilize one or two or three major methods of treatment.

Dr. Rubin Flocks (Iowa City, Iowa): I think that Dr. McDonald's paper is a very important contribution, and I want to congratulate him.

Dr. Emmett's paper likewise is a very important contribution, and I only wish that it would have been possible, in retrospect, to have statistics in regard to metastases to the regional lymph nodes. In his group of cases, labeled those without metastases, although obviously inoperable clinically for the most part at least, among them are certain ones that actually do have metastases. I am sure of that, as a result of our findings in the retropubic exploration of over 500 patients of this type.

We found in this group of a little over 500 patients, approximately 40 per cent of regional lymph node involvement, and the incidence of regional lymph node involvement varied with the size of the prostate as palpable rectally. Therefore, it might be possible, for example, if we have the actual records on these patients of Dr. Emmett's, to determine not only how they were related in regard to the grade of carcinoma but also the size of the lesion when first seen and the probable incidence of lymph node metastases.

For example, in this group of 500 patients, which I just mentioned, we found that none had bony metastasis. None of them had elevated acid phosphatase determinations. We found that the incidence of regional positive lymph node was 40 per cent. We found that the incidence in the small lesions was much lower, between 15 per cent and 20 per cent, and in the large ones, close to 90 per cent. Thus, we could elaborate further and get more information with regard to hormonal control in that group of patients, which Dr. Emmett so well analyzed, if we knew the size of the local lesion, and then we could interpolate the possibility of lymph node metastasis.

In regard to the paper of Dr. O'Conor, the question arises as to whether we are going to emphasize the negative or the positive. Emphasis belongs on the last case reported, the patient who has gone almost five years and seems to be doing all right. We have patients, who seem to be doing all right over five years now, and the smaller the lesion, the more likely you are to get a good distribution and to get the effects that you wish.

I wish to stress, in addition to emphasizing that last case of Dr. O'Conor, the fact that the total volume injected into the lesion is of great importance. We found that when we endeavored to inject lymph nodes and tried to inject areas of bladder cancer that we got the same effect, the same thing that Dr. O'Conor got in his dogs and in the cutaneous nodules. We were unable to secure decent distribution.

On the other hand, in the prostate, we got much better distribution if we used a very low volume with the same dose; in other words, injecting 1 cc, carefully placing the needles—and that is extremely important. One cubic centimeter containing, let's say, 35 or 45 millicuries, is a lot different from injecting one containing 10 or 15 millicuries. We made both blood and liver studies during the injection and afterwards, and the amount that left the prostate was tremendously different, depending on the volume that was injected. It is important to accurately place the needles in the prostate. At any rate, I think that everything Dr. O'Conor showed was correct. It followed along our earlier experience, but our results as we have progressed have tended to accentuate the positive, the type of thing that Dr. O'Conor mentioned in this last case.

Dr. Donald F. McDonald (Rochester, N. Y.): I should mention that there is relationship between dithizone and zinc metabolism and that dithizone was selected because it is a known zinc chelator. We have recently completed some studies that show that when zinc is given in addition to dithizone, the effects of the dithizone are not negated. The dithizone does not exert its antiprostatic effect because of its effect on zinc metabolism in the body.

Dr. John Emmett (Rochester, Minn.): There are just three points that I should clear up. The first is that all of these cases I was talking about were what you have been referring to as inoperable. They were all done previous to 1952. Dr. Culp came to the clinic in 1952, and that is when he began doing some radical perineal prostatectomies; before that, none were done at the clinic.

Dr. Flocks mentioned some of our patients whom we call non-metastatic. I tried to emphasize that. We are dealing with full grown clinical carcinoma of the prostate. Perhaps, I should use the term distant metastasis. I am trying to show that if you get these patients before distant metastases develop, it is still possible to get some

very striking results, especially with early orchiectomy.

Finally, Dr. Flocks, about the size of the prostate. Those data are terribly inaccurate when you are looking over a large series of cases. We tried to get that information. You would be surprised. A fellow says the prostate is grade 3 and hard. The medical consultant says the prostate is normal, that it feels okay to him. The urologist comes along, says it is carcinoma, and calls for a section. Another one comes along and says, "I am not sure." It is just like deciding whether this girl is pretty or isn't.

DR. JOSEPH H. KIEFER (Chicago, Ill.): Are you now recommending that this grade 1 group with the 70 per cent survival submit to radical prostatectomy?

DR. EMMETT: You mean the occult group?

DR. KIEFER: Yes.

DR. EMMETT: I should say I have never advised radical prostatectomy.

DR. JOHN LATTIMER (New York, N. Y.): What was your conclusion about stilbestrol, the combination of orchiectomy plus stilbestrol, or orchiectomy alone?

DR. EMMETT: Our findings don't always show that stilbestrol is effective. That is about the only thing we got different from Reed's study. When I send a patient home with orchiectomy, I give him stilbestrol.

Dr. Kiefer, I answered you rather facetiously. I think that our figures show that of the 113 cases of occult carcinoma, grade 1, the patients have normal survivals, whether you give them stilbestrol or you don't. Sometimes you say it won't hurt them to take stilbestrol, and send them home; we have no evidence to show that it helps.

DR. JOSEPH H. KIEFER (Chicago, Ill.): You are advising radical prostatectomy?

DR. EMMETT: I think that shows it isn't necessary.

DR. KIEFER: That is the group of what is said to be the ideal case.

DR. EMMETT: I take it from them.

DR. VINCENT J. O'CONOR (Chicago, Ill.): I would like to call attention to our loose nomenclature when we speak of metastases from neoplastic disease. In the light of our modern cytological studies I believe we are going to have to revise our opinions as to how we determine metastatic disease in patients who have had carcinoma of any type. Careful blood studies recently in many clinics have shown a very high incidence of circulating cancer cells in the blood when x-rays of the bones and soft tissues fail to show any evidence of metastatic disease. In our clinic recently the resident desired to study the effects of estrogen in individuals who had no evidence of bone marrow involvement, secondary to cancer of the prostate. In obtaining the bone marrow studies on these patients in whom there was no evidence of x-ray metastases, a very high percentage of them had cancer cells in the bone marrow, which was removed for study.

DR. J. HARTWELL HARRISON (Boston, Mass.): Were they anemic?

DR. O'CONOR: Many of them were. We are studying them carefully with sternal and iliac specimens of bone marrow. I believe that we should revise our statements when we say there are no metastases in a patient by saying there is nothing demonstrable or no reason for evidencing metastases.

I am quite aware of Dr. Flocks' suggestion as to increasing the quantity of isotopes to cubic centimeter in injecting cancer of the prostate. At the present time we are averaging 25 millicuries per cubic centimeter. Originally we used from 3 to 5 millicuries per cubic centimeter which was his own original suggestion. Krebiozen has been used by a number of men in our hospital only because the family insisted that it be given members of their family who were afflicted with cancer which had not responded to other measures. So far we have not seen a single evidence where krebiozen did any good.

POST-PROSTATECTOMY URINARY INCONTINENCE: EXPERIENCE WITH A GROUP OF DIVERSE SURGICAL TECHNIQUES

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The normal act of micturition is of not much concern to the healthy man, who accepts this gift of nature with no more thought than he gives to his daily ablutions. However, when the obstructive phase enters the picture and he realizes that an operation is imminent, his thoughts turn to the anticipated successful surgical outcome. Some with knowledge gained from reading or from the experience of friends fear the possibility of incontinence. It is the problem of this group of unfortunates who have suffered the indignities of iatrogenic urinary incontinence that forms the basis of our report.

Our last report concerning this subject was presented before this Association in 1956, when the use of the anteropubic fascial sling was discussed. We are not pleased with this operation, although colleagues have personally reported some favorable results. We have not employed it since then. We consider this operation lacking in physiologic conformity. In this group of 6 patients to be discussed, we have used techniques previously reported by others. In one of these techniques we have, unsuccessfully on three occasions, made an innovation without detracting from the basic principle upon which the original Keyes-Hayes operation was based. Two of this present group to be reported are "hang-overs" from the original group of eight reported upon in 1956, while four are new patients. All 6 patients had true surgical post-prostatectomy incontinence of urine. Five had been subjected to transurethral prostatic resection, one to suprapubic prostatectomy.

THE PROBLEM OF THE PATIENT

Experience with this group has impressed upon us that there is no unhappier person than the constant dribbler. His psychologic reaction is not one of attunement to his new environment, even though he seemingly has accommodated to the inconvenience of the situation. He blames the original surgeon and tends to become a medical shopper both of which demand an invocation of the code of ethical practice. The problem is doubly enhanced in the senile group in which co-operative effort is difficult to obtain for the interpretation of the positive or negative results after an operation. These are desperate men. They will not only accept single operative procedures without question but ask for multiple corrective operations in their pursuit of a drier status. Promises of the efficacy of surgical correction cannot and must not be made. The patient must be told the details and the facts of the very limited success of surgical correction. A facetious definition of true surgical urinary incontinence is "That certain post-prostatectomy leakage in his patient which has made the surgeon feel sorry for himself."

THE CRITICAL AREA: THE MEMBRANOUS URETHRA

It would appear that our knowledge concerning the mechanism of incontinence is incomplete. If this were not so we would not have such an array of diverse surgical techniques embodying different ideas of implementing urinary control. An analysis of the type of incontinence under discussion following our various commonly employed methods of prostatectomy would lead one to suppose that the critical area of injury probably resides in the membranous urethral component. Many of our textbooks incorrectly portray the anatomic relationship, especially in the sagittal section, between the apex of the prostate and urogenital diaphragm. The apex of the prostate is usually depicted as hugging the posterior layer of the urogenital diaphragm whereas these are actually separated by a small, well defined segment of membranous urethra, known as the posterior or proximal portion of the membranous urethra. This fact becomes obvious on rectal examination and is well demonstrated during retropubic and perineal exposure. The distal portion of the membranous urethra resides within the layers of the urogenital diaphragm and represents the area of the external urinary sphincter. The membranous urethra is therefore composed of two important and fundamental segments.

When we speak of urinary continence following prostatic surgery I believe we all accept the present concept of its motivation as residing in the striated musculature of the external urethral sphincter. In 1952, Elliot provided evidence from anatomical studies that just distal to the prostate a considerable condensation of smooth muscle fibers encircles the urethra. These lie between mucosa and striated muscle and, along with the connective tissue, make up the bulk of the urethral wall. In his summary he stated, "A revised concept of the external urethral sphincter is presented, in which the sphincter is regarded as being composed essentially of smooth muscle, which aids primarily in a reflex or unconscious manner to maintain urinary continence. The striated urethral muscle functions as an accessory and alone does not constitute the external sphincter." Kuss of Paris, one of our corresponding members, and Mathieu in 1955 wrote in the same vein concerning the role of the smooth muscle and that continence was dependent on this ring or cuff of tissue lying between prostate and the urogenital diaphragm.

These anatomic facts help to elucidate the mechanism of incontinence. An explanation is given as to why the incontinent male volitionally can control his leakage, and as soon as he dispenses with volitional effort why he cannot involuntarily prevent dripping. An explanation is imparted to the reading of post-prostatectomy urethrograms, notably transurethral resection, wherein the urine is shown held back at the apex of the prostatic urethra rather than at the urogenital diaphragm. Another example of its mechanism may be studied in the ruptures of the true external urethral sphincter secondary to fractures of the pelvic bone. In the senior author's clinic (C.A.W.U.) such a case was recently seen. Surgical care was prompt, extensive damage was noted but no incontinence followed.

In our formative surgical years, we all can remember having removed too much apical tissue at the time of enucleation or not having paid enough respect to the membranous urethra at the time of perineal section. In transurethral resection the verumontanum is an important landmark and represents the distal limit of resection. In studying incontinent cases after resection, the verumontanum is sometimes found to have been removed, while in other cases it is present and it is difficult to visualize any gross defective reason for incontinence. Damage to the proximal membranous urethra is a more logical explanation than to its distal portion or site of the true external sphincter. It is our thought that if resection were carried so far forward, extravasation and rectal perforation would be more conspicuous as complications.

The length of the posterior membranous urethra is strikingly demonstrated during resection by withdrawing the instrument to the external sphincter area and peering towards the verumontanum, as pressure is made rectally on the urethra at the prostatic apex. Rolnick and Arnheim in 1949 contributed a worthwhile article on this subject. In all specimens studied they found the average distance from verumontanum to external sphincter to measure 0.9 cm.

In 1944 Uhle and Erb reported 3 cases of reconstruction of the membranous urethra. All had been victims of an automobile accident, and each had suffered a fractured pelvis and urethral trauma. In 2 cases dense strictures were cored out of the true external sphincter area. In one the length of the posterior membranous urethra was sufficient to bring anteriorly through the site of the true external sphincter for anastomosis to the anterior urethra. In the second, the bulb of the urethra was inserted through the tunnel of the external sphincter without severance of the membranous posterior urethra. Healing was prompt. No incontinence was encountered. These 2 cases are mentioned to demonstrate the length and mobility of this portion of the urethra and that surgical revision is possible without incontinence resulting. These facts may be of import if a satisfactory surgical technique in this particular area is developed some day for post-prostatectomy incontinence. The recent work of Lapides is outstanding and germane to the subject.

TYPES OF OPERATION FOR INCONTINENCE

It can be axiomatically stated that not one surgical technique exists for consistent salvage of the post-prostatectomy incontinent patient. These techniques can be grouped into four general classes used individually or in combination:

1) *Operations of revision.* This group refers to the creation of vesical neck or urethral stenosis by incision, or wedge excision.

2) *Operations of compression.* The mechanical effect of pressure on the urethra in this group

is made by a sling, muscular or fascial in origin, which does not completely surround the urethra. Pressure is made in the urethra in one direction producing angulation.

3) *Operations of constriction.* The physical principle of action in this group is pressure on all quadrants of the urethra thus creating an artificial sphincter. Sphincteric action may be obtained by a) muscular constriction such as that induced by the gracilis transplant, or b) stenotic constriction obtained by encircling the urethra with a nonresilient substance such as chromicized ribbon catgut. Millin in 1947 reported some sixteen successful operations. We have used Millin's technique only once in an octogenarian with initial good results; even attacks of retention were induced. This man had marked sacculation of the pendulous urethra from having worn a Cunningham clamp. Within two months he reverted to his original incontinent status. No stricture of the urethra resulted.

4) *Operations of support.* In this group would be included such operations as the plication procedures wherein the transversus perinei muscles, the ischiocavernosus, and the levator ani muscles are used. The retropubic suspension of the prostate and vesical neck, according to the technique of Marshall, Marchetti and Krantz, would be placed in this group. We used this technique in one case and the result was a total failure.

In 5 cases we used the technique of Keyes and Hayes. In three of these we added an innovation of our own in an attempt to achieve more elevation and compression of the membranous posterior urethra and prostatic apex. This consisted of inserting a globular shaped pad of fascia and fat in the region of the prostatic apex. This tissue is obtained from the abdominal wall and is fixed in position just before the last suture is tied, which brings together the levator ani and bulb of the urethra. None of these 3 patients had a satisfactory result although one stated that he was slightly improved. He also made two interesting observations to the effect that 1) he could stop his urinary stream more abruptly and 2) that if we had given him a little more elevation he would have been able to keep dry.

Quakels of Brussels in 1955 reported 2 cases of incontinence following suprapubic prostatectomy. Continence was restored in each instance by injecting two to three ounces of paraffin through the perineum about the membranous urethra.

One of our two patients in whom no elevating tissue had been used in the Keyes-Hayes procedure was normally continent for three days following removal of his catheter. On the fourth day he slipped and fell, becoming totally incontinent again. Our deduction from this incident is that the levator ani muscle is not a good one for plication as the muscle fibers can readily tear apart.

SUMMARY

We have commented on the role of the membranous urethra in the control of urinary continence after prostatectomy.

The various surgical techniques employed for the correction of urinary incontinence have been grouped into four general categories and reference made to their failure of achievement.

Our experience with a group of diverse procedures in 6 patients has been presented.

4) We are hopeful for the future. We feel that a gradual synthesis of investigative efforts will eventuate in the establishment of a physiologic technique applied in that certain portion of the urethra where the reflex of continence is initiated.

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DISCUSSION

Dr. J. Hartwell Harrison (Boston, Mass.): I very hesitatingly come forward. I have, perhaps naively, continued to be an advocate of total prostatectomy in selected cases. I would like to make the public admission that I certainly always look at the patient and wonder how he is going to tolerate incontinence if he is incontinent after total prostatectomy. It seems to me we still have that complication, but I think much less often than previously.

I would like to pay tribute to the late Dr. Samuel A. Vest in his efforts to control this, and I think he added a great deal to the management of this problem. We have made, perhaps, a slight modification of the closure, which I believe has been helpful. It seems to me, also, Dr. Uhle, that the vesical neck is very important and that the reconstruction of the vesical neck is very important in avoiding incontinence following total prostatectomy.

After completion of total prostatectomy, the bladder is open. We close from above downward reconstructing the vesical neck just distal to the trigone; in other words, trying to reconstruct as closely physiologically the vesical neck to what it was originally, about 26 mm. in circumference. Then, the vesical neck comes up, so. In these 40-odd cases we have done, twice I have occluded the ureters and had to go back and relieve that occlusion, because the vesical neck was too tightly angulated. In one instance, the right ureter was divided and had to be reimplanted. The reconstruction of the vesical neck is an important feature in avoiding incontinence.

Dr. Wyland Leadbetter (Boston, Mass.): I suppose we are all interested in urinary incontinence because we see it and can rarely cure the patient. In the last few years, I have made various attempts at treating men with urinary incontinence utilizing techniques somewhat different than those Dr. Uhle has suggested. One of the few patients with whom I have had success was a man with urinary incontinence following transurethral resection. Endoscopy revealed that a groove had been cut through the sphincter between 6 and 8 o'clock, but the remainder of the sphincter appeared intact and actively tonic. I felt that if I could dissect out the scar which involved the area of urethra in the triangular ligament that I might get a result. Therefore, I operated upon this man by perineal exposure, found a good deal of scar around the apex of the prostate and the membranous urethra. This was excised. The area of urethra involved was removed also, and then the urethra pulled together with very tiny catgut sutures. This man has had complete relief of his incontinence. However, since then I have tried this on other occasions without getting results. Perhaps my technique wasn't good.

Most incontinence in males that I have seen has not resulted from perineal prostatectomy but from suprapubic prostatectomy and in studying these cases, it has seemed to me that the cause of the trouble has been scarring and fixation of the musculature at the apex of the prostate and in the triangular ligament, perhaps because infection gravitated onto the urogenital diaphragm above. I am sure that in most of these cases the musculature in the urogenital diaphragm was not injured at the time of operation. Perhaps a vesical and prostatic urethral suspension or lysis might improve or correct incontinence in these patients.

I would mention another case in which incontinence was cured by total prostatectomy. This patient had undergone a suprapubic prostatectomy, followed by total incontinence and after watching him for a period of time, I did a radical perineal prostatectomy. In this case there was considerable scar about the urogenital diaphragm. I made no effort to anastomose the prostate to the membranous urethra but brought sutures through the perineum. The patient has had a very satisfactory result.

I mention these cases because they represent my experience in trying to correct incontinence in the male after some type of prostatectomy.

Dr. John K. Ormond (Pontiac, Mich.): I just wish to mention my experience with Lowsley's puckering operation. I used this method of anastomosing urethra and bladder in most of the 42 radical prostatectomies I have done, and had only two instances of incontinence.

Dr. J. A. C. Colston (Baltimore, Md.): I should like to emphasize what Dr. Harrison has said about the function of the internal

sphincter. Some years ago I saw a case of carcinoma of the urethra which arose in the membranous urethra and extended from the apex of the prostate just through the external sphincter. It was obvious that if this entire lesion was excised with a margin above and below, the whole external sphincter would have to be removed, so I explained to the patient that he would certainly be totally incontinent. Exposing the prostate through the perineum, the distal half of the prostate together with the whole membranous urethra and the external sphincter was removed in one piece; but, of course, the so-called internal sphincter was left intact. To my surprise, after the wound had healed and the catheter had been removed, this patient had partial urinary control and could start and stop the flow of urine, although an apparatus for urinary incontinence was necessary.

This case has emphasized to me the fact that the so-called internal sphincter plays a very definite part in the control of urination, but it cannot be depended upon for complete urinary control.

Dr. Reed Nesbit (Ann Arbor, Mich.): I think in a discussion of this sort where we are using the term "external sphincter," we should remember that my associate, Dr. Lapides, demonstrated when all the skeletal muscle of the body had been completely paralyzed, the person still has perfectly normal urinary control, so the external sphincter is not necessary for the control of urine. It does have the effect of cutting off urination quickly. The patient, who has the muscle paralyzed, can cease urinating in the middle of the stream only after the lapse of a few seconds. The man who does not have paralysis of this external sphincter can stop urination immediately on command.

President Taylor: It was my impression that the man could void independently of his voluntary muscle.

Dr. Nesbit: That is right.

President Taylor: Isn't he apt to lose it now and then?

Dr. Nesbit: The subjects who were examined were able to initiate and stop urination voluntarily. They emptied the bladder completely. The matter of partial incontinence when the patient was on his feet was impossible to determine, because these patients were all lying flat under the conditions of the experiments.

Dr. David M. Davis (Philadelphia, Pa.): Years ago we constructed a little device consisting of a short piece of metal tubing attached to a very fine, slightly curved metal rod. With this in place the internal sphincter was put out of action. We had another catheter, which was simply cut off square at the end. This catheter could be placed with the end in the prostatic urethra thus putting the external sphincter out of action. We found that either in a lying or standing position the patient could control his urine perfectly whichever sphincter was out of action. I throw this observation in for what it is worth, you must take it from there.

HYPOTENSIVE ANESTHESIA FOR PROSTATIC SURGERY

FRANK C. HAMM

Brooklyn, N. Y.

Dr. Hamm's manuscript was not submitted for publication.

DISCUSSION

DR. DONALD F. MCDONALD (Rochester, N. Y.): I would like to ask Dr. Hamm a question. Did you measure the blood loss during prostatectomy under "hypotensive anesthesia" and compare it with patients not so treated? Is it possible that your enthusiasm for reducing the number of blood transfusions might have changed the incidence of blood transfusion from 15 per cent to 4½ per cent?

DR. GRAYSON CARROLL (St. Louis, Mo.): I would like to ask Dr. Hamm what is his detailed method of administration for getting his hypotension—the percentage you use?

DR. HAMM: How we attain hypotension?

DR. CARROLL: Yes.

DR. HAMM: In the majority, we just let it drop down.

DR. CARROLL: What drop down and to what percentage?

DR. HAMM: Let's say the average patient comes in with a pressure of 140. We let it drop down to between 90 and 100.

DR. CARROLL: What drug do you use?

DR. HAMM: We don't use anything. If the pressure tends to come down by itself, we just let it drop.

DR. CARROLL: If it doesn't do that?

DR. HAMM: Spinal anesthesia in itself will produce hypotension. The big trouble is that the average anesthetist will put neo-synephrine in. Get your anesthetist to eliminate your basal substances.

DR. RUBIN FLOCKS (Iowa City, Iowa): Do you raise the pressure at the end?

DR. HAMM: No.

DR. FLOCKS: Don't they bleed afterwards?

DR. HAMM: No.

DR. FLOCKS: When does the blood pressure come back up?

DR. HAMM: It comes up slowly. We keep the patients in the resection room for at least half an hour to an hour after each operation to watch them. The only thing we use to regulate blood pressure is infusion. We speed up our infusion.

DR. GRAYSON CARROLL (St. Louis, Mo.): I had the impression that in the 5 per cent which don't come down, naturally you use neosynephrine.

DR. HAMM: Yes. It is in an infusion bottle of 1 mg. You have it fixed up to a tube, and you have your plain fluid in one flask and the mixture in the other. It is easy to regulate. Blood pressures have to be taken almost constantly.

DR. CARROLL: That answers my question.

DR. HAMM: To answer the first question, we did not measure blood loss, and there probably is a factor there in my desire to eliminate the blood transfusions, plus a greater care in technique. We are deliberately doing everything we can to reduce blood loss and to avoid transfusion. There are other factors that work here.

DR. FRANK HINMAN, JR. (San Francisco, Cal.): I just want to ask a question. Dr. Hamm's type of hypotensive surgery is not quite what I understood it to be. He deals in 60 systolic. This is sedation type. I wonder if Mr. Turner-Warwick has had any experience in true hypotensive anesthesia.

DR. HAMM: If you get down to the 50 levels, you are going to get into trouble. Our patients are old arteriosclerotics. I refer you to an article in the BRITISH JOURNAL OF UROLOGY in Decembet 1957. They don't go that low. I think that is extremely dangerous.

MR. R. TURNER-WARWICK (London, England): Since you asked, I will tell you what Sir Eric Riches thinks about this. He usually does a retropubic prostatectomy. His anesthetist is Dr. Bernard Johnson, who uses fluothane, and he likes to retain the blood pressure. He feels that the blood lost during the operation is minimal. The blood pressure comes up again.

DR. GRAYSON CARROLL (St. Louis, Mo.): Is it

not true that these tranquillizers, thorazine and the like, will reduce blood pressure rather dangerously at times? Have you had experience with giving any of those tranquillizers prior to operating procedure?

DR. HAMM: We have not used thorazine.

DR. C. D. CREEVY (Minneapolis, Minn.): Our anesthesiologists are very reluctant to do anything to lower the blood pressure of a surgical patient. I believe that they are conditioned by the fact that our general surgeons do a great many very long, very serious operations in which prolonged hypotension can be a real threat to the patient's life. When the blood pressure during a prostatic operation at the University of Minnesota is too high, one can with difficulty persuade the anesthetists to give 5 to 10 mg. thorazine intravenously. This has a transitory but favorable effect in lowering the blood pressure; indeed, it is somewhat like arfonad in that the patient becomes sensitive to changes in position. However, when the blood pressure offers a real problem, I can usually persuade them to use 0.1 per cent arfonad as a slow drip and I feel that this is a very important means of saving blood and relieving strain upon the blood bank. I agree with Dr. Hamm.

However, I feel that a systolic pressure between 90 and 100 mm. mercury is low enough and that genuine hypotensive anesthesia, such as is discussed in the literature, offers too much of a hazard to the elderly arteriosclerotic patient.

THE ROLE OF THE UROLOGIST IN THE DIAGNOSIS AND TREATMENT OF HERMAPHRODITISM

WILLIAM WALLACE SCOTT

Baltimore, Md.

Dr. Scott's manuscript was not submitted for publication.

DISCUSSION

DR. ROBERT S. HOTCHKISS (New York, N. Y.): Recently a child was born at Bellevue Hospital with ambiguous sex. It became apparent that some time would be required to do the necessary cytological and hormonal tests to ascertain the correct sex of the child. This delay often causes great anxiety because relatives and friends constantly inquire whether the new child is a girl or a boy. The Puerto Rican mother devised a plan to avoid commitment to the relatives of the sex of the child while these investigations were being made. She said to her friends, "I have had twins, one is a boy and one is a girl. Both are sick and one may die." The surviving twin would be the boy or girl according to the results of the hospital tests.

DR. ROBERT GARRETT (Indianapolis, Ind.): I wonder if Dr. Scott would comment on indications for a clitoridectomy. What do you feel should be done in some of the pseudohermaphrodites with adrenal hyperplasia?

DR. SCOTT: It is not always necessary to remove the clitoris in a female pseudohermaphrodite. I said nothing about the use of sex hormones at puberty, but I don't think that one can predict with any degree of accuracy the necessity for a particular hormone. We simply postpone this until the patient goes through puberty and then recommend the use of androgenic or estrogenic substances as the need arises.

DR. JOSEPH KIEFER (Chicago, Ill.): I would like to differ. Our experience is that the clitoris doesn't return to normal female size within any short time. When you are raising a child, what makes a child a boy to the other children, to the family, and to himself? His phallus, and a girl doesn't have one. If they have this large clitoris, then you are trying to fit them into the female psychologic pattern, and they do not work together. We start them on the cortisone therapy, and within a relatively short time, and during infancy, we do reconstruction of the vulva.

DR. SCOTT: I would like to ask about numbers.

DR. KIEFER: I have done about 15. These have been done mostly in the younger age group. Our experience was that the clitoris did not return to normal female size.

DR. GEORGE CAHILL* (New York, N. Y.): I have seen quite a few of these within the last 30 years or more. I have seen these clitorises that were about as big as those of a 12 or 14-year-old boy with an erection. I have seen them in little children three or four years old, probably five or six inches long. I have photographs of them. Even though you start to reverse the appearance of that child, backed by adequate therapy, that clitoris is a disturbing factor. We have reached the conclusion that we should get rid of that clitoris, because it is an object of curiosity to every other little girl. Many of these cases have interesting histories. I have had two boys raised as girls. They both had penises and uteruses, a gonad on one side and an ovary on the other, raised in girls' high schools and then sent away to girls' schools in which they had opportunity of sexual intercourse with males, while in these schools; and they immediately wanted to become males. We transferred them to different schools, removed their uteruses, and brought their undescended testes out. They have been males ever since. One of them is married. When they reach adult life, they should be allowed to take the sex they wish. We have had others who were perfect males as far as function was concerned and deliberately masqueraded for obvious purposes. They were purely male hermaphrodites, who had to shave. They would be admitted frequently on the female ward, take the hand of the nurses, where their true sex was disclosed.

DR. JOHN K. LATTIMER (New York, N. Y.): As Dr. Cahill has said, we have been trying to

* Deceased.

dispose of the enlarged phallus, and recently we have been doing something that I am sure isn't original with us, but is, in effect, "recessing" the clitoris. The child we operated upon last week had a large phallus that looked something like your thumb, with an introitus below, a vagina at the back and the urethra immediately above it. We divided down a bit. We removed the skin of the phallus by making an incision around the base, then a circumcizing incision, and made the glans smaller by taking off parts of it around the corona, and then end up with a relatively narrow strip of erectile tissue down the center. If you free it up well, you can tunnel it down through a buttonhole and bring through a tip of the glans just above the urethra. The Mayo Clinic has made a survey of the distribution of the end organs of sensations in the glans phallus, and has found that the greatest concentration is around the corona of the glans rather than at the tip. Nevertheless, we remove the corona because we must make the glans smaller. The skin makes a ridge in many of these cases similar to the labia minora, and the outer skin tends to roll together. This recessing of the phallus under the skin has been cosmetically very satisfactory. The question is whether, as they grow older, they will continue to have erections, and this ridge of tissue under the skin will be troublesome to them, as claimed by Dr. Scott's medical colleagues. Nevertheless, we have tried this technique and find that it works pretty well. I think we will continue to do it in more cases until we build up some experience. We then close the previous site of the phallus as a vertical linear closure.

Dr. Frank Hinman, Jr. (San Francisco, Cal.): The problem of the clitoris is the chance of its reappearing as a penis during the life of this patient—Dr. Kiefer is quite correct; the family is very disturbed about this organ. The sooner it is gotten rid of the better. It has been my experience, too, although in not as great a series as either Dr. Kiefer or Dr. Scott, that these clitorises do not immediately shrink down as soon as cortisone therapy has been started. But, perhaps, more important than that, is the corollary of it. We are living in a troublous time. Are we sure that 10 years from now or 20 years from now the cortisone factories are still going to be operating, and that these patients are going to have a regular supply of cortisone? My guess is, as a relatively young man, that they will not. There is a reasonable possibility. This is like Jekyll and Hyde. These patients are now Dr. Jekyll, but the moment their cortisone is turned off, they become Mr. Hyde and will go through this horrible transformation almost as in the movies, becoming hairy, and, more important, growing clitorises capable of recurrent erections. I think the idea of getting rid of the clitoris is best. Sensation is minimal, and adult women move this sensation into the vagina anyway.

The second point I would like to make is, I think, concerning a misconception. Dr. Scott didn't mention it, because he didn't have time. We are always called upon to do vaginograms if, in some way, examining the external genitalia is going to tell us something about the sex of these patients. The point rather is to look at the phallus and ask, "Is it possible to reconstruct it?"

We are dealing here with a continuum of intersexuality, and the female moves over into the male side, and vice versa, depending on what time during embryologic life intersexual influences take place, and that there is no way of saying, "Here is a cervix; therefore, it must be a female," or "There is no cervix; therefore, it is a male." Vaginograms, to my knowledge, have no real diagnostic value.

Frederick Howard's contribution is that the lesser degrees of hypospadias are associated with lesser degrees of müllerian duct differentiation. This happens in reverse in patients with female pseudohermaphroditism. The groups that are exceptions to this can be recognized by other ways. The blonde Venus type, which Dr. Scott showed you in his picture with the short vagina, and certain other distinct groups are not confused with the usual intersex patient. Certainly the diagnosis will not be forthcoming from study of the vaginograms.

FOLLOWUP REPORT ON A CASE OF BILATERAL PAPILLARY CARCINOMA OF THE RENAL PELVIS

J. A. CAMPBELL COLSTON, SR.

From the James Buchanan Brady Urological Institute, Johns Hopkins Hospital, Baltimore 5, Md.

Every surgeon knows, of course, that followup studies in all cases, especially if dealing with malignant disease, should be pursued as accurately as possible and every effort should be made to obtain the subsequent history of the patient's progress.

In 1954 I reported before this society a case of bilateral renal papillary carcinoma treated by transpelvic electroresection of a tumor in a solitary functioning left kidney, and right nephrectomy 4 years later. Aside from the operation on a tumor in a solitary kidney, the case represents the very unusual finding of bilateral renal papillary carcinoma. At the time of the report in 1954 the patient was free from symptoms and the pyelogram of the left kidney (the only functioning kidney), in which the pelvic tumor had been destroyed by electrocoagulation, was normal and there was no evidence of any suspicious filling defects. This patient has just recently been examined and in view of the fact that it might be interpreted from the literature that a "cure" had been obtained, it seemed essential that the results of followup studies and further treatment should be published.

A brief summary is necessary to understand the subsequent course of treatment. This patient who is now 66 years old was subjected to an abdominal hysterectomy elsewhere for fibroids in 1943. In the course of the operation the right ureter was probably injured and urine drained from the vagina for 4 months. When drainage ceased excretory urograms showed no function of the right kidney. The left kidney was considered normal. She had a mild episode diagnosed as right pyelitis associated with some flank pain during her postoperative course. The patient remained in good health until 1950, at which time she passed blood in the urine over a period of about eight hours. A left retrograde pyelogram revealed a filling defect in the lower portion of the renal pelvis. The patient's relatives were told that a tumor was present in her only remaining kidney and that no operation could be done.

On admission to the Johns Hopkins Hospital an intravenous pyelogram showed a filling defect in the lowermost portion of the pelvis and of the lower calyx of the left kidney. There was no function on the right side. On August 23, 1950 through a left flank incision the pelvis, which was extrarenal, was exposed, opened and two small sessile tumors protruded, apparently arising in the upper portion of the lower calyx or in the infundibulum. These tumors were easily destroyed with the cutting and the coagulating current and 25 per cent solution of podophyllin was then applied to the tumor-bearing area. The patient's postoperative course was uneventful. Histological examination revealed a papillary tumor which had not infiltrated the muscular wall of the pelvis.

Over the next 3 years the patient was in excellent health and free from symptoms, and retrograde pyelograms during this time showed no evidence of any filling defect in the ureter or pelvis; but there was some narrowing of the infundibulum of the inferior major calyx, which was interpreted as scarring as a result of the electrocoagulation of the tumor.

The patient returned in November 1953 complaining of a mass in the right side of the abdomen which had been present for 3 weeks. On examination the left kidney was not palpable or tender. In the right upper quadrant extending to just below the umbilicus was a large, smooth, freely movable, nontender mass. Blood chemistry studies and hemogram were entirely normal. An intravenous urogram showed no secretion on the right side and the left pelvis and calyceal systems and ureter were considered normal with no evidence of filling defect. It was impossible, of course, to catheterize the right ureter. A tentative diagnosis of right closed hydronephrosis was made. On December 12, 1953 the abdomen was explored through a right rectus incision. A brownish-blue retroperitoneal cystic mass was immediately noted and recognized as a hydronephrotic kidney with a greatly dilated, tortuous ureter below it. A nephrectomy and partial ureterectomy were carried out without incident.

FIG. 1. Preoperative retrograde pyelogram shows considerable dilatation of pelvis and calyces. Kink in ureter indicates redundancy, below which ureter is dilated down to two typical filling defects. Ureter below filling defects is normal.

There was no evidence of intra- or retroperitoneal or liver metastasis. The left kidney felt normal. The patient's postoperative course was uneventful.

The operative specimen consisted of a large hydronephrotic sac with no remaining renal parenchyma. In the lower calyx there was a 2 by 2 cm. papillary tumor. Microscopic sections showed a fairly well differentiated papillary carcinoma with no direct invasion of the muscularis of the pelvic wall. From the studies of these two operations it was evident that a very unusual condition of bilateral papillary carcinoma of the pelvis of the kidney was present. The duration of the tumor in the right kidney is, of course, a matter of speculation. After the kidney underwent atrophy as a result of the ureteral injury, it is probable that the small pelvic tumor began to bleed resulting in distension of the already dilated kidney pelvis and the appearance of the mass on the right side. Since the removal of the hydronephrotic right kidney which contained a papillary tumor, the patient remained in good general health and retrograde left pyelograms twice a year showed no evidence of any filling defect in either the renal pelvis or the calyces or the ureter.

In March 1958 she was treated by antibiotics for influenza and on several occasions passed a small amount of blood in the urine. A cystoscopic examination showed a small tumor which was destroyed by electrocoagulation. During October and November she again passed blood on several occasions; cystoscopy was repeated and another small bladder tumor was destroyed. As these procedures were carried out in another hospital and the small tumors were apparently completely destroyed, there are no microscopic specimens available.

In February 1959 retrograde studies showed two filling defects in the left ureter (fig. 1). The patient was admitted to the Johns Hopkins Hospital. Physical examination was essentially normal except that a well healed right rectus scar was present, but no mass could be felt. There was also a well healed left lumbar scar, and again no mass was palpable. There was no abdominal tenderness or mass. An old, well healed midline suprapubic scar was present. The urine showed a trace of albumin, microscopically an occasional white cell and 1–2 red blood cells per high power field. Blood chemistry and hemogram were normal. Phenolsulfonphthalein excretion studies showed 4 per cent the first half hour, 18 per cent the second half hour, 12 per cent the third half hour and 10 per cent the fourth half hour, a total of 44 per cent.

On cystoscopic examination bladder capacity was 600 cc. The internal orifice was essentially normal. The right ureteral orifice was inactive. The bladder wall showed early trabeculation; no cellules, diverticula, stone or ulcer; nowhere could any evidence of tumor be seen. An intravenous urogram showed that the calyces of the left kidney were moderately blunted and the infundibulum to the lower calyx was very narrow, probably as a result of scar tissue. However, the outlines of the calyces, pelvis and upper ureter were everywhere quite smooth. There was no indication anywhere of a filling defect or irregularity. The ureter was moderately dilated and there was a redundant kink just below the ureteropelvic junction. At the brim of the pelvis the ureter showed two fuzzy, irregular filling defects, typical of tumor of the ureter. The ureter below the area in which the filling defects were present was of normal caliber down to the bladder.

A diagnosis of ureteral tumor was made, probably implantation from the original pelvic tumor. As it was obvious that the increasing obstruction, due to the ureteral tumor, would eventually destroy the patient's only remaining kidney, an operation was decided upon. Several choices of operative technique were considered: 1) Excision of the tumor bearing area with reanastomosis of the ureter. The x-ray films showed that the upper ureter was redundant, so that simple excision and reanastomosis was considered the method of choice. 2) The other possibilities were the excision of the whole lower ureter, including the tumor-bearing area, and construction of a sleeve from the bladder with anastomosis to the stump of the upper ureter, and 3) complete excision of the whole lower ureter and implantation of the proximal ureteral stump in an ileal loop.

On March 2, 1959 the ureter was exposed through a long left paramedian incision. The ureter was easily identified as it crossed the iliac vessels and immediately one could feel two small masses in the lumen. The ureteral wall nowhere showed any evidence of infiltration or thickening. It was freely mobilized, a clamp placed at a point 2 cm. above the tumor-bearing area and the ureter cut across. The lower ureter, after a clamp had been placed 2 cm. below the tumor-bearing area, was similarly severed and the portion of ureter about 3 cm. in length containing the tumors was removed. The upper ureter was then carefully mobilized taking advantage of the redundancy of the upper portion, and it was found easily possible to bring together the proximal and distal stumps of the ureter without tension. A small ureterotomy incision was made 3 cm. below the distal stump of the ureter and a size 10 soft rubber catheter passed up the distal

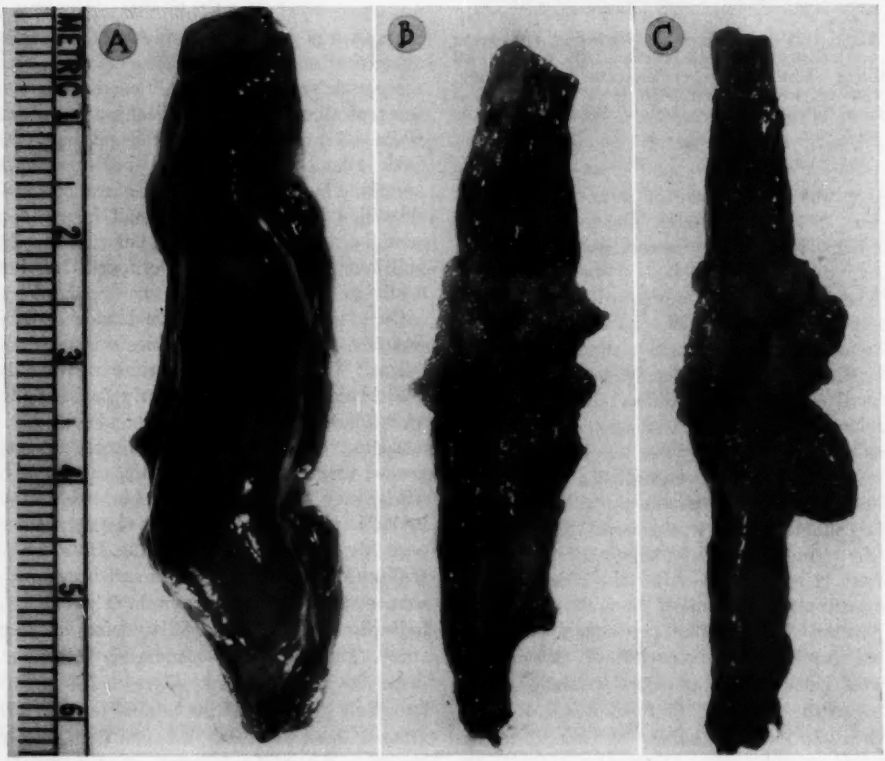

FIG. 2. *A*, operative specimen shows masses in ureteral lumen. No evidence of gross infiltration of ureteral wall. *B* and *C*, ureter opened showing extension of tumor but no gross evidence of deep infiltration.

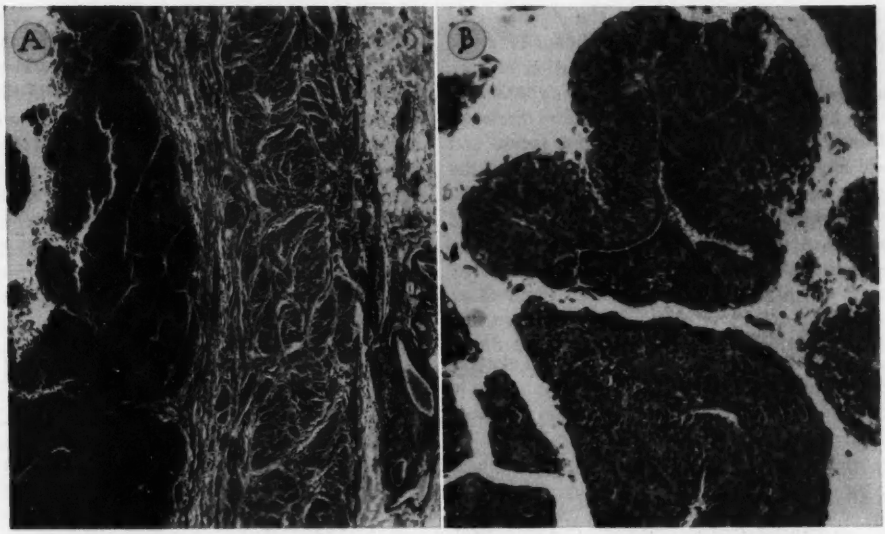

FIG. 3. Photomicrographs of tumor. *A*, low power shows no evidence of infiltration into submucosa or muscularis. *B*, high power shows typical papillary carcinoma.

portion into the proximal portion and carried up as far as the pelvis. The ureteral stumps were then brought together with three or four stitches of four zero chromic catgut and the ureter replaced in the wound. A Penrose drain was placed down to the site of the anastomosis and the incision closed in layers.

The patient had no postoperative complications. The splinting catheter drained clear urine. Five days after the operation, when the urine had completely cleared, a specimen was sent to the cytological laboratory for a Papanicolaou stain. The results were reported as negative for malignant cells. Phthalein excretion through the ureteral splint before it was removed showed: first half hour, 40 per cent; second half hour, 17 per cent; third half hour, 15 per cent; fourth half hour 10 per cent, a total of 82 per cent. The splinting catheter was removed on the tenth day, after which the patient voided urine normally and there was no leakage through the wound. She was discharged on the fourteenth day in excellent condition.

Pathological examination of the operative specimen showed no gross infiltration of the ureteral wall (fig. 2, *A*). When the ureteral wall was opened a sessile papillary tumor was seen (fig. 2, *B* and *C*), with again no evidence of deep

FIG. 4. Postoperative intravenous urogram. Dilatation of pelvis and calyces has disappeared. Narrowing of infundibulum to upper and middle calyces, which has been noted in previous pyelograms, is still present, probably due to scar tissue where original tumor was destroyed. Lumen of ureter below crest of ilium can be quite well seen, and there is no evidence of constriction.

infiltration. Microscopically, the tumor consisted of a typical papillary carcinoma of grade 1 or 2 with no evidence of infiltration of submucosa or of muscle (fig. 3).

An intravenous urogram done before discharge showed that the dilatation of the pelvis and calyces had almost entirely disappeared and the ureter had almost returned to normal size. The dye could be seen coursing through the site of the anastomosis, but the lumen at this point was quite small (fig. 4).

DISCUSSION

Vest has discussed the treatment of small tumors of the ureter by ureterotomy and electrocoagulation under direct vision. Considerable criticism has arisen about this method of treatment, so at present it is the consensus that in the presence of a ureteral tumor a complete nephroureterectomy should be done. When the ureter was exposed in the case under discussion, it seemed evident that the safest method to employ was to remove the tumor-bearing area of the ureter between the clamps which would prevent any possibility of spilling malignant cells in the wound.

The causative factor in the appearance of the two small ureteral tumors 8 years after the tumor of the pelvis, which were microscopically identical, remains a matter of speculation. Did these ureteral tumors arise as an implantation from the original pelvic tumor, which might have recurred, or did they arise from a carcinogenic agent secreted in the urine? My own conclusion would be that the latter theory is more tenable because the pelvic tumor had been destroyed 8 years ago, and especially because the intravenous urogram now shows no evidence of any filling defect or distortion in the region of the pelvis or calyces.

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DISCUSSION

Dr. Wyland Leadbetter (Boston, Mass.): Our experience indicates that upper urinary tract papillary tumors are becoming more frequent. During the last 3 years, in addition to several unilateral tumors, we have seen 4 patients with bilateral ureteral or pelvic tumors associated with bladder tumors. We shall have to be prepared to study bladder tumor cases carefully for ureteral and pelvic tumors and plan proper operative procedures to handle the situation.

To illustrate the problem, the first patient I remember was a woman upon whom I did cystectomy for multiple and rapidly recurring tumors of the bladder. At the time I operated upon her, she had an obvious tumor in the right ureter. I, therefore, did a cystectomy and right nephro-ureterectomy. Some months later, she was found to have a tumor in the upper left ureter and renal pelvis. I operated upon her, removed the tumor and coagulated the base; following this she lived 2 years without difficulty, but finally died of a recurrence of tumor in her pelvis.

The last patient is one who is presently under treatment, having undergone within the last month a left nephro-ureterectomy for extensive tumor of the ureter but who has, in addition, a papillary tumor involving the right ureteropelvic junction. This patient presents a problem in therapy. It has been my intent to see if one can resect the area of ureter involved doing an end-to-end anastomosis or substituting the ureter with ileum.

I should be interested to know whether urologists, in general, are seeing more of these tumors. Our experience would indicate that one must obtain intravenous pyelograms rather frequently in checkup studies on patients with papillary tumors of the bladder.

Dr. Vincent O'Conor: In the first hundred years of the Massachusetts General Hospital, there was only 1 patient with ureteral tumor.

Dr. Leadbetter: I think we have 25 cases

CARCINOMA OF THE PENIS

LUIS A. SANJURJO AND BERNARDINO GONZÁLEZ FLORES

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To make another report on 24 case histories of carcinoma of the penis may seem of little clinical value specially when extensive and very complete publications are available on the subject and when no particular features in relation to this disease are to be contributed.

Our main interest has been directed towards finding the true incidence of the disease in Puerto Rico. We were surprised to discover that it is low in spite of the fact that roughly 80 to 90 per cent of the male population has not been circumcised. It has not been until recent years that circumcision is being carried out on a wide scale both in charity and private patients.

For the sake of information it can be stated that the incidence of carcinoma of the penis seems to vary from one country to another. Ngai[1] claims it to be 18.3 per cent in China, 4.9 per cent in continental Europe, 1.3 per cent in Great Britain and 2 per cent in America. According to Dean,[2] carcinoma of the penis represents 2 per cent of all tumors of the urogenital tract.

The age at which this tumor usually develops ranges from 40 to 60 years but one case has been reported of a patient 2 years old. One of our patients was 91 years old (table 1).

Several etiological factors have been brought to the consideration of the medical profession such as implantation on the penis from carcinoma of the cervix, trauma, occupation, heredity, constitutional and venereal diseases. However, not enough evidence has been found in support of these theories which have been largely discarded.

Possibly everyone agrees on the fact that the retention of smegma is the most frequent cause for the development of the disease on the uncircumcised individual. It is worth noting that among certain animals which secrete an excessive amount of smegma, carcinoma of penis is extremely prevalent. A long or tight prepuce was found in 92 and 98.9 per cent of the cases studied by Dean and Ngai,[3] respectively.

According to various reported series, carcinoma of the penis is more prevalent among whites than among negroes. It is almost nonexistent in orthodox Jews and among Mohamedans who practice ritualistic circumcisions, but frequent among the Hindus who do not follow this practice. In certain sections of India carcinoma of the penis was found to be 10 per cent in 797 cancer patients.[4]

It is apparent that circumcision, when performed during the first days of life, prevents cancer, but when the procedure is done later in life a malignant tumor may develop as late as 40 years. In case 18 in this series carcinoma developed 56 years after the patient was circumcised. It is also known that a malignant growth has developed at the site of the circumcision scar.

The disease, which may develop as a variable sized papule, nodule, scaly patch, ulcer, or on a plaque of leukoplakia, can be readily discovered by the patient whose prepuce can be easily retracted behind the glans penis. In those with nonretractable prepuces their attention is brought later when marked secondary infection supervenes and the pain and foul-smelling, bloody and dirty looking discharge are present. As some patients are accustomed to frequent bouts of acute or subacute balanoposthitis, sometimes they pay no attention to the change in character of the discharge.

Very frequently the lesions under a tight prepuce are discovered at the time of doing a dorsal slit or a circumcision. Whatever the appearance of the lesion, it is usually located on the glans penis, coronal sulcus, reflected layer of the prepuce, external urinary meatus and, rarely, on the skin of the penile shaft. If the disease pro-

[1] Ngai, S. K.: Squamous cell carcinoma of penis among Chinese. Am. J. Cancer, **19:** 259, 1933.

[2] Dean, A. L.: Epithelioma of the penis. J. Urol., **33:** 252, 1935.

[3] Herbut, P. A.: Urological Pathology. Philadelphia: Lea and Febiger, 1952, pp. 855–865.

[4] Lowsley, O. S. and Kirwin, T. J.: Clinical Urology, 3rd ed. Baltimore: Williams and Wilkins Co., 1956, pp. 134–137.

gresses it involves the whole glans penis which is destroyed, producing narrowing of the external meatus and the formation of urinary fistulas when the urethra is involved. Complete obstruction never occurs.

Protected by Buck's fascia the corpora cavernosa are involved late, but when this natural barrier is penetrated dissemination occurs promptly.

Grossly the lesion may appear nodular, fungating or ulcerating. Most of the penile cancers are epidermoid carcinoma grade 2 or 3. The growth may spread to every tissue and organ in the body through the lymph channels either by direct penetration of the lymph vessels or by embolization. The superficial inguinal and subinguinal lymph nodes are first invaded followed by the iliac group of nodes. Both sides may be equally affected. The inguinal lymph nodes may be found enlarged; this is not always due to metastasis but the result of accompanying secondary infection. On the other hand, glands to which the tumor has spread may not be enlarged. Occasionally anaplastic tumors are encountered which are rapid in growth and dissemination.

All penile lesions having an obscure etiology and which resist conventional treatment should be suspected of being malignant and a generous specimen, which should include the base of the lesion, taken for microscopic study.

The cellular changes due to concomitant secondary infection may be granulomatous in type and at times more than one biopsy is required to detect malignant degeneration. This is extremely important in view of the medicolegal implications that may arise inasmuch as the usual treatment is surgical and mutilating.

The treatment of carcinoma of the penis is usually surgical; either conservative, if the lesion is small and well localized; or radical, when emasculation is necessary. Superficial small lesions may be treated by radiation with radium with satisfactory results. However, post-radiation reactions may be of extreme severity making necessary partial amputation at a latter date to relieve pain and discomfort.

A guillotine type of amputation, 1 inch from the border of the lesions, is usually recommended with preservation of about ¾ inches of urethra which should project beyond the stump of the corpora cavernosa and everted to prevent stricture formation.

Partial or radical ilioinguinal gland dissection has been advocated and should be carried out.

In the only patient with carcinoma of the penis found in 1944 during World War II at the 161st General Hospital, malignant tumor spread was found in only one of the glands removed. This patient, 28 years of age at the time, is still alive and well (case No. 80910, pathological report C-377, U. S. Army). Had gland dissection been omitted the patient most probably would be dead by now.

A short analysis of the San Juan City Hospital series reveals that what has been exposed is fully substantiated.

Table 1 shows that the average age at the time of operation was 54 years. The youngest patient was 30 years old and the oldest 91.

TABLE 1. *San Juan City Hospital cases*

Case No.	Age	Race	Operation		
			Partial amputation	Amputation and inguinal nodes disection	Amputation and radical ilioinguinal and femoral nodes disection
1	47	W	—	×	—
2	53	W	×	—	—
3	30	C	—	—	×
4	91	W	×	—	—
5	58	W	×	—	—
6	58	W	—	—	×
7	43	C	—	—	×
8	40	W	—	×	—
9	57	W	—	—	×
10	46	W	×	—	—
11	52	C	—	—	right side
12	89	W	×	—	—
13	66	W	—	—	right side
14	64	W	—	right side	—
15	34	W	—	×	—
16	75	W	—	×	—
17	44	W	—	×	—
18	65	W	×	—	—
19	60	W	—	—	×
20	49	C	—	×	—
21	?	W	×	—	—
22	49	C	×	—	—
23	48	C	—	—	×
24	36	W	—	—	×

There were 18 white patients against 6 negroes which amounts to a white to negro ratio of 3:1.

All our patients were treated surgically. A simple partial amputation of penis was done in 8 patients. Partial amputation of penis and inguinal nodes dissection were performed in 7 patients and amputation of penis and radical ilioinguinal and femoral nodes dissection in nine. In most instances the operative procedure was performed in two stages: 1) the amputation and a unilateral node dissection followed a week later by 2) node dissection on the other side. However, the last few patients underwent a one stage surgical intervention with gratifying results.

Table 2 presents the pathological reports and the survival rates. All the patients had epidermoid carcinoma, mostly grade 1 and 2. Sixteen underwent lymph nodes dissection and of these only 2 cases (Nos. 17 and 20) revealed metastases.

Seven patients (29.2 per cent) have survived over five years. So far, four (16.7 per cent) have died. Case 12 died in the hospital 12 days after simple amputation of the penis as a result of cardiovascular accident, sepsis and malnutrition. Cases 17 and 20, with regional lymph nodes metastases, survived over one year but eventually died of carcinomatosis. Case 22 died of carcinoma of the lung, 6 years 4 months after simple amputation of penis.

Table 3 demonstrates that 21 patients (87.5 per cent) had congenital phimosis on arrival at the hospital. In three (Nos. 5, 10 and 18) circumcision had been done prior to development of the carcinoma. Cases 5 and 10 underwent circumcision two and three years respectively prior to admission while in case 18 the circumcision

TABLE 2. *Pathological report and survival rate*

Case No.	Penis	Lymph Nodes	Survival	Cause of Death
1	Epidermoid carcinoma grade 1	Negative	7 yrs. 9 mos.	—
2	Epidermoid carcinoma	—	13 yrs.	—
3	Epidermoid carcinoma grade 2	Negative	6 yrs. 3 mos.	—
4	Epidermoid carcinoma grade 2	—	1 yr.	—
5	Epidermoid carcinoma grade 2	—	1 yr.	—
6	Epidermoid carcinoma grade 1	Negative	2 yrs. 7 mos.	—
7	Epidermoid carcinoma grade 1	Negative	2 yrs. 8 mos.	—
8	Epidermoid carcinoma grade 1	Negative	3 yrs. 2 mos.	—
9	Epidermoid carcinoma grade 2	Negative	4 yrs.	—
10	Epidermoid carcinoma early	—	4 yrs. 5 mos.	—
11	Epidermoid carcinoma grade 1	Negative	3 mos.	Sepsis, malnutrition
12	Epidermoid carcinoma grade 4	—	12 days	Cardiovascular accident
13	Epidermoid carcinoma grade 4	Negative	1 yr. 6 mos.	—
14	Epidermoid carcinoma grade 1	Negative	1 yr. 7 mos.	—
15	Epidermoid carcinoma grade 2	Negative	7 yrs.	—
16	Epidermoid carcinoma grade 1	Negative	8 yrs. 8 mos.	—
17	Epidermoid carcinoma grade 2	Metastases to left inguinal nodes	1 yr. 4 mos.	Carcinomatosis
18	Epidermoid carcinoma grade 2	—	10 mos.	—
19	Epidermoid carcinoma grade 2	Negative	8 yrs. 3 mos.	—
20	Epidermoid carcinoma grade ?	Metastases to inguinal nodes	2 yrs. 5 mos.	Carcinomatosis
21	Epidermoid carcinoma	—	?	—
22	Epidermoid carcinoma grade 1	—	6 yrs. 4 mos.	Carcinoma of the lung
23	Epidermoid carcinoma grade 2	Negative	7 mos.	—
24	Epidermoid carcinoma grade 3	Negative	5 mos.	—

TABLE 3. *Incidence of phimosis*

Case No.		Location of Tumor	Duration of Lesion
1	Phimosis	Glans	4 mos.
2	Phimosis	Glans	6 mos.
3	Phimosis	Prepuce and glans	3 mos.
4	Phimosis	Prepuce	2 yrs.
5	Circumcision done 2 yrs. prior to admission	Glans	1 yr.
6	Phimosis	Shaft of penis near frenum	1½ yrs.
7	Phimosis	Prepuce	2 mos.
8	Phimosis	Glans	Not specified
9	Phimosis	Glans and prepuce	6 mos.
10	Circumcision done 3 yrs. prior to admission	Glans	2 yrs.
11	Phimosis	Prepuce	Not specified
12	Phimosis	Glans	3 mos.
13	Phimosis	Glans	4 mos.
14	Phimosis	Glans	6 yrs.
15	Phimosis	Glans	3 mos.
16	Phimosis	Glans	4 yrs.
17	Phimosis	Glans	2 mos.
18	Circumcision done at 9 yrs. of age	Glans	6 mos.
19	Phimosis	Glans and prepuce	6 mos.
20	Phimosis	Glans	1 mo.
21	Phimosis	Glans	2 yrs.
22	Phimosis	Glans and prepuce	2 yrs.
23	Phimosis	Glans	7 mos.
24	Phimosis	Prepuce	4 mos.

was performed 56 years before the onset of carcinoma.

The tumor involved the glans penis in 18 patients (80 per cent) and the rest were limited or extended to the prepuce.

The average duration of the lesion in the penis before the patient sought medical advice was 14 months.

From this study we have concluded that carcinoma of the penis is less prevalent in Puerto Rico than we have heretofore suspected. Among 117,924 consecutive admissions to the San Juan City Hospital from 1946 to February 1959, carcinoma of the penis was found in 24 instances (0.02 per cent). During this same period of time about 60,000 visits are recorded in the urology outpatient clinics of this hospital.

These figures represent a fairly good cross section because this hospital not only admits patients from the metropolitan area (625,000 inhabitants) but also many patients with complicated medical and surgical problems from all over the island.

In a review of 4932 records on male private patients carcinoma of the penis was found in one occasion (0.02 per cent). This patient however was neither born in nor a resident of Puerto Rico, but came to the island for treatment.

Curbelo,[5] in 26 years, has seen only two private patients with carcinoma of the penis. At the Bayamón District Hospital in a 20 year period during which there were 121,577 admissions to that institution, he found 100 (.08 per cent).

Colón,[6] in his excellent discussion on the subject reported 145 cases (3.6 per cent) of carcinoma of the penis in 4023 cancer patients admitted to the Hospital of Onchology in Puerto Rico in an 11 year period.

His figures may appear very high but one must consider that at this medical center only cancer-proven or cancer-suspected patients are referred for diagnosis and treatment not only from the metropolitan area but also from the rest of the island.

During World War II, in the period comprised between 1942 and 1945, over 17,000 soldiers were admitted to the 161st General Hospital. Troops were mainly Puerto Rican and continental Americans, a few European and South Americans. One soldier among 17,000 admissions (.006 per cent) was found to have carcinoma of the penis.

SUMMARY AND CONCLUSIONS

A review of the factors responsible for carcinoma of the penis has been discussed.

The incidence of carcinoma of the penis in the

[5] Curbelo, P. G.: Personal communication.

[6] Colón, J. E.: Carcinoma of the penis. J. Urol., **5**: 702–708, 1952.

two largest and most active hospitals on the island has been presented as well as among private patients.

In spite of the fact that in the past, circumcision was rarely carried out on the island and that 80 to 90 per cent of the male population has not been circumcised, the general incidence of penile cancer is extremely low.

We are unable to explain the reason or factors.

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DISCUSSION

DR. LUIS A. SANJURJO (Santurce, Puerto Rico): There is nothing to add except in relation to inguinal gland dissection. In our practice if the lesion is small, radical inguinal gland dissection, as has been illustrated on the film, may have some beneficial effect. If the lesions are large, usually metastasis has already occurred, and additional surgery, besides partial amputation, may prove valueless.

RADICAL PENECTOMY: ANATOMY AND TECHNIQUE

WILLIAM H. BOYCE

Winston-Salem, N. C.

Dr. Boyce's presentation was in the form of a motion picture.

DISCUSSION

DR. CHARLES UHLE (Philadelphia, Pa.): What about lymphedema of the leg?

DR. BOYCE: There has been no persistently troublesome lymphedema of the leg. In 3 patients in this series, only one has had noticeable edema; this was in the left leg. I think this is due to the primary healing without the long-term superficial infection that accounts for this absence of edema. Primary healing should permit persistence of collateral lymphatics, whereas the development of massive lymphedema of the lower extremities is commonly associated with some type of inflammatory disease which may well block all lymphatics in the area.

DR. JOHN K. ORMOND: Just before I left the Henry Ford Hospital, I reviewed the cases of cancer of the penis which had been seen there in the 37 years of my service, and found 13 cases. In contrast to this, during the 2 years that I was in India we were never without at least one case on our wards, and usually more. In our region it is the fourth most commonly seen cancer. It is seen exclusively in Hindus and never in Moslems. Hindus are not universally circumcized, but the Moslems are ritually circumcized at the age of 12.

DR. BOYCE: I think diagnosis of metastases by biopsy of a single node or even bilateral inguinal nodes has proven most ineffective in our series. In practically every reported series, the number of these patients who eventually die of metastatic cancer, but in whom there were no obvious metastases to the superficial inguinal nodes, would seem to be in accord with the unreliability of single-node biopsies.